THE IMPACT OF SYSTEMIC CORTICAL ALTERATIONS ON PERCEPTION

Zheng Zhang

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Approved by:

Mark A. Tommerdahl, Ph.D.

Oleg V. Favorov, Ph.D.

Robert G. Dennis, Ph.D.

Jeffrey M. Macdonald, Ph.D.

Denniz Zolnoun, M.D.

ABSTRACT

ZHENG ZHANG: The Impact of Systemic Cortical Alterations on Perception
(Under the direction of Dr. Mark A. Tommerdahl)

Perception is the process of transmitting and interpreting sensory information, and the primary somatosensory (SI) area in the human cortex is the main sensory receptive area for the sensation of touch. The elaborate neuroanatomical connectivity that subserves the neuronal communication between adjacent and near-adjacent regions within sensory cortex has been widely recognized to be essential to normal sensory function. As a result, systemic cortical alterations that impact the cortical regional interaction, as associated with many neurological disorders, are expected to have significant impact on sensory perception. Recently, our research group has developed a novel sensory diagnostic system that employs quantitative sensory testing methods and is able to non-invasively assess central nervous system healthy status.

The intent of this study is to utilize quantitative sensory testing methods that were designed to generate discriminable perception to objectively and quantitatively assess the impacts of different conditions on human sensory information processing capacity. The correlation between human perceptions with observations from animal research enables a better understanding of the underlying neurophysiology of human perception. Additional findings on different subject populations provide valuable insight of the underlying mechanisms for the development and maintenance of different neurological diseases.

During the course of the study, several protocols were designed and utilized. And this set of sensory-based perceptual metrics was employed to study the effects of different conditions (non-noxious thermal stimulation, chronic pain stage, and normal aging) on sensory perception. It was found that these conditions result in significant deviations of the subjects' tactile information processing capacities from normal values. Although the observed shift of sensory detection sensitivity could be a result of enhanced peripheral activity, the changes in the effects of adaptation most likely reflect changes in central nervous system. The findings in this work provide valuable information for better understanding the underlying mechanisms involved in the development and maintenance of different neurological conditions.

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CHAPTER 1

INTRODUCTION

Perception is the process of transmitting and interpreting sensory information, and the primary somatosensory (SI) area in the human cortex is the main sensory receptive area for the sensory of touch. A series of neurophysiological observations have demonstrated that well controlled stimuli delivered to the skin, which can promote cortical regional interactions, induce dynamic changes of neuronal activity in SI cortex. For example, Simons et al. (2005) investigated the optical response of squirrel monkey contralateral SI to vibrotactile stimulation (25Hz), and found that as the stimulus amplitude was increased, the activity within the activated region of SI cortex progressively increased although the spatial extent of the activated region remained relatively constant. Analogously, human perceptual studies have demonstrated that these localized increases in the magnitude of the SI cortical response paralleled the changes in the ability of human subjects to distinguish between different intensities of skin stimulation (Francisco et al. 2008). Additionally, in another study, Simons and colleagues (2007) discovered that more intense and longer duration stimuli would result in more spatially resolved activation, due to the lateral inhibitory effect that spatially funnels the responding SI neuronal population. Findings of human psychophysical studies have shown that the ability of a subject to accurately localize and discriminate a flutter stimulus on the skin is determined by the locus and clarity of the neuronal population response within the topographically organized SI network (LaMott and Mountcastle 1975, 1979). As a result,

systemic cortical alterations that impact such cortical-cortical interaction would have significant impact on sensory perception.

There is substantial evidence that many neurological disorders are associated with systemic central nervous system alterations, and these systemic cortical alterations, whether it is neurodevelopmental, neurodegenerative, pharmacological or trauma induced, lead to significant changes in sensory perception. For example, subjects with autism typically have increased sensitivity to sensory stimuli of many modalities (Kanner 1943; O'Riordan and Passetti 2006). Although they are not significantly different from typical controls in amplitude discriminative capacity (Tannan et al. 2008), they demonstrate a reduced response to repetitive stimulation – or less of an adaptive response (Tannan et al. 2008; Tommerdahl, Tannan, Cascio, et al. 2007). In this case, the hyper-excitability observed in autism has been speculated to be the result of deficient inhibitor circuitry, possibly linked to a genetic disparity in GAD (Glutamic acid decarboxylase) which is responsible for normal conversion of glutamate to GABA (Gamma-aminobutyric acid) neurotransmitter. Additionally, non-specific hyersensitivitiy has been characterized in patients suffering from chronic pain (e.g. fibromyalgia, back pain, neuropathic pain etc.), and it has conventionally been attributed to changes in 'central sensitization' caused by the chronic pain state.

Because of the close correlation between perception and healthy brain status, sensory assessment could be considered as an efficient approach to evaluate sensory function. However, traditional sensory testing methods mainly employ single-site stimulation which is not ideal for the study of cortical-cortical interactions. Additionally, these tests that rely on threshold testing or tests of sensitivity predominantly measure functions of the peripheral nervous system, and the small signal to noise ratio of near-threshold stimulation normally

induces large inter-subject variability. In our research group, we have developed unique quantitative sensory testing methods that are based on information obtained from neurophysiological studies of the non-human primate cerebral sensory cortical response to a variety of modes of natural skin stimulation. The methods were designed to generate measurable perception and enable objective evaluation of the elaborate neuroanatomical connectivity that subserves the neuronal communication between adjacent and near-adjacent regions within sensory cortex that is widely recognized to be essential to normal sensory function. Although this intra-cortical communication involves numerous mechanisms, the tests that we developed appear specifically sensitive to the status of mechanisms currently believed by many to play major roles in the disorders of sensory cortical information processing in a number of neurological disorders – i.e., neurotransmission mediated by the inhibitory neurotransmitter gamma aminobutyric acid (GABA) and by N-methyl-d-aspartate (NMDA) receptors, and interactions/interdependencies between neurons and glial cells.

The studies described in this dissertation have focused on utilizing quantitative sensory testing methods to assess human sensory information processing capacity under different conditions. The correlation between human perceptions with observations from animal research enables a better understanding of the underlying neurophysiology of human perception. Additional findings on multiple subject populations have led to novel insights about the perceptual changes that occur with systemic alterations of cerebral cortical function, and provided useful information of the underlying mechanisms for the development and maintenance of different neurological diseases.

In chapter 2, a modified amplitude discrimination test was designed which is able to assess the effects of spatial acuity on amplitude discrimination and provide a better means of

objective and quantitative assessment of spatial discrimination capacity. In these studies, a set of sensory-based discrimination metrics was employed to study the impact of different conditions (non-noxious thermal stimulation, chronic pain, and normal aging) on sensory perception. In chapter 3, the effects of non-noxious thermal stimulation on tactile discriminative processing capacity were evaluated. It was determined that the subject's performances in the tests that involve both temporal and spatial summation of sensory information are significantly impacted by elevation of skin temperature, and these perceptual changes might reflect a shift in the balance of cortical excitation and inhibition caused by non-noxious thermal stimulation. This metric could provide a means for assessing central sensitization in patient populations that have dysfunctional mechanisms for mediating pain-touch interactions without the delivery of painful stimuli. In chapter 4, altered central sensitization in subgroups of women with vulvodynia was studied. The results suggest that chronicity of vulvar pain leads to changes in the effect of adaptation on tactile perception, which reflect an altered central sensitization linked to dysfunction in CNS inhibitory pathways. It was proposed that vulvodynia syndromes are likely to be triggered by peripheral factors in the skin or underlying musculature, and with time and chronicity, varying degrees of central dysregulation may develop. In chapter 5, the cortical-cortical interactions in the healthy aging population are presented. The subject's performance in a set of sensory-based discrimination tests demonstrated that although age-related degradations was shown during peripheral –mediated testing, effects of adaptation (cortical plasticity) was maintained in normal aging and compensates for both anatomical and physiological losses that have been shown to naturally occur with age. The major target of this study is to establish baseline data

to enable the launching of a more prospective longitudinal study for the diagnostic screening of the early detection of Alzheimer's disease.

CHAPTER 2

DEVELOPMENT OF A QUANTITATIVE METHOD FOR DETERMINING SPATIAL DISCRIMINATIVE CAPACITY

This work in this chapter has been reported in: Zhang Z, Tannan V, Holden J, Dennis RG, Tommerdahl M. (2008) A quantitative method for determining spatial discriminative capacity. Biomed Eng Online. Mar 10; 7:12.

2.1 Abstract

The traditional two-point discrimination (TPD) test, a widely used tactile spatial acuity measure, has been criticized as being imprecise because it is based on subjective criteria and involves a number of non-spatial cues. The results of a recent study showed that as two stimuli were delivered simultaneously, vibrotactile amplitude discrimination became worse when the two stimuli were positioned relatively close together and was significantly degraded when the probes were within a subject's two-point limen. The impairment of amplitude discrimination with decreasing inter-probe distance suggested that the metric of amplitude discrimination could possibly provide a means of objective and quantitative measurement of spatial discrimination capacity.

A two alternative forced-choice (2AFC) tracking procedure was used to assess a subject's ability to discriminate the amplitude difference between two stimuli positioned at near-adjacent skin sites. Two 25 Hz flutter stimuli, identical except for a constant difference

in amplitude, were delivered simultaneously to the hand dorsum. The stimuli were initially spaced 30 mm apart, and the inter-stimulus distance was modified on a trial-by-trial basis based on the subject's performance of discriminating the stimulus with higher intensity. The experiment was repeated via sequential, rather than simultaneous, delivery of the same vibrotactile stimuli.

Results obtained from this study showed that the performance of the amplitude discrimination task was significantly degraded when the stimuli were delivered simultaneously and were near a subject's two-point limen. In contrast, subjects were able to correctly discriminate between the amplitudes of the two stimuli when they were sequentially delivered at all inter-probe distances (including those within the two-point limen), and improved when an adapting stimulus was delivered prior to simultaneously delivered stimuli.

Subjects' capacity to discriminate the amplitude difference between two vibrotactile stimulations was degraded as the inter-stimulus distance approached the limit of their two-point spatial discriminative capacity. This degradation of spatial discriminative capacity lessened when an adapting stimulus was used. Performance of the task, as well as improvement on the task with adaptation, would most likely be impaired if the cortical information processing capacity of a subject or subject population were systemically altered, and thus, the methods described could be effective measures for use in clinical or clinical research applications.

2.2 Introduction

The capacity of a human subject to spatially resolve tactile stimuli delivered to the skin has traditionally been investigated by measuring the smallest distance between two

tactile stimuli at which they evoke two distinct percepts (Weber 1846). Typically, the two-point discrimination (TPD) test has been widely used in clinical diagnoses as well as scientific studies. Along with its popular applications, however, TPD has been criticized as being imprecise for several reasons. First, it has been discussed that as the distance between two points varied, the perceptual patterns may gradually change. Tawney (Tawney 1895) stated that there were some intermediate sensations between the perception of one point and that of two points. As a result, the "first perception" of two points measured as TPD might provide an inaccurate measure of the minimum space of tactile spatial resolution whereas the "middle sensations" may represent the actual consciousness of spatiality (Lundborg and Rosen 2004; Tawney 1895). Second, since different subjects adopted distinct criteria for defining two points, the responses were based to a great extent on the subject's experience. As a result, a large variability between subjects has been observed. Craig and Johnson (Craig 2000) quoted a study in which Valentin and collaborators found that the TPD measures were highly inconsistent across all subjects, with nearly a four-fold difference in thresholds observed on the same region of the body. Third, traditional TPD tests involve a number of non-spatial cues which confounded subject discrimination. For instance, Titchener (Titchener 1916) found that in the objective TPD tests which employed one-point as well as two-point stimulation, subjects felt that the perceived intensity of one point was always stronger than that of two points. The above-described arguments suggest that the subjective TPD threshold might not provide a consistent and reliable measure of tactile spatial resolution. For these reasons, we sought to develop a more objective measure of spatial discrimination capacity.

Alternative methods have been developed to substitute for the traditional TPD test. Tannan et al. presented a novel Two-Point Stimulator (TPS) which was capable of delivering

two identical vibrotactile stimuli simultaneously at two discrete skin sites with variable distances on a trial-by-trial basis (Tannan, Dennis, and Tommerdahl 2005; Tannan, Dennis, and Tommerdahl 2005; Tannan, Whitsel, and Tommerdahl 2006). By way of automated stimulus control and delivery, the TPS enabled a faster and more accurate administration of two-point measurement than previous TPD devices. However, in these particular studies, the discrimination test was still based on personal subjective criteria. Similarly, a number of other studies have demonstrated that grating orientation discrimination is a well-established and reproducible measurement of tactile spatial acuity on the finger pad (Johnson and Phillips 1981; Craig 1999; Grant et al. 2006). However, it was argued that there might be substantial anisotropy on the finger pad which was related to spatial sensitivity and might permit subjects to discriminate grating orientation on the basis of intensive rather than spatial cues (Craig 1999). Additionally, a subject's orientation discrimination capability is typically assessed by interpolating the groove width with 75% correct responses (Hodzic et al. 2004; Van Boven et al. 2000). Thus, in order to have enough values for interpolation, the percentages of accurate responses of several gratings with different groove widths need to be measured for each subject.

Recently, Tannan et al. (Tannan, Dennis, et al. 2007) measured subjects' amplitude discrimination between two simultaneous 25 Hz vibratory stimuli delivered to the dorsum surface of the hand. The result indicated that amplitude discrimination became worse when the two stimuli were positioned relatively close together and was significantly degraded when the probes were within a subject's two-point limen. This impairment of amplitude discriminative capacity with decreasing inter-probe distance led the authors to hypothesize that the metric of amplitude discrimination could provide a means of objective and

quantitative measurement of spatial discrimination between two-point on the skin. Such a measure could be used for objective evaluations of subject populations whose cortical information processing capacity is systemically altered or different from healthy control populations. In addition to assessing simple spatial discriminative capacity, slight modifications of stimulus conditions could reveal other aspects of a subject's central nervous system, based on predicted cortical-cortical interactions that result from these different stimulus conditions.

To investigate the above-described hypothesis, a modified amplitude discrimination protocol was used to assess a subject's ability to discriminate a constant amplitude difference between two 25 Hz flutter stimuli as the stimuli were tracked to more proximal skin sites on the hand dorsum. Although comparable to an amplitude discrimination task which measures the minimum discriminable amplitude difference between two simultaneously delivered stimuli (Tannan, Dennis, et al. 2007), the current protocol was unique in that the amplitude difference was constant and well above the average amplitude difference limen (reported in previous studies (Tannan, Dennis, et al. 2007; Tannan, Simons, et al. 2007)), and the inter-stimulus distance was modified on a trial-by-trial basis based on the subject's performance. The inter-stimulus distance metric obtained from the study appears to be fairly robust across the subjects studied thus far (i.e., low variance between individual performance) and can be obtained relatively quickly (about three minutes).

2.3 Methods

Ten subjects participated in this experiment. They were naïve both to the study design and issue under investigation. All experimental procedures were reviewed and approved in advance by an institutional review board.

The tactile stimuli used in this study were sinusoidal vertical skin displacements delivered by a novel dual-site vibrotactile stimulator (details about the CM-1 stimulator are described in a recent report; (Tannan, Dennis, et al. 2007)). The CM-1 dual-site stimulator is capable of delivering two tactile stimuli simultaneously or sequentially at discrete skin sites with independent control of vibration frequency, amplitude, and phase, while providing accurate control of stimulus's timing and location.

During the experiment, the subject was seated in a chair with his/her left forearm on the table positioned comfortably to allow unimpeded access of the stimulator to the center of the dorsal surface of left hand (Figure 2.1). To ensure a stable hand position for the duration of the experiment, the subject was instructed to place their palm on the table surface as flat as possible, and a bead bag was applied to immobilize the wrist. The reasons that we selected the hand dorsum to receive the stimulation are: 1) the innervation density across this skin region remains relatively constant; 2) the surface is easily accessible and permits convenient stimulator placement; 3) use-dependent plasticity is minimized (i.e., the hand dorsum is, for the most part, used the same amount in daily activity by all subjects); and 4) it permits positioning of the subject's arm and hand in a comfortable and stable position for the full duration of an experimental session.

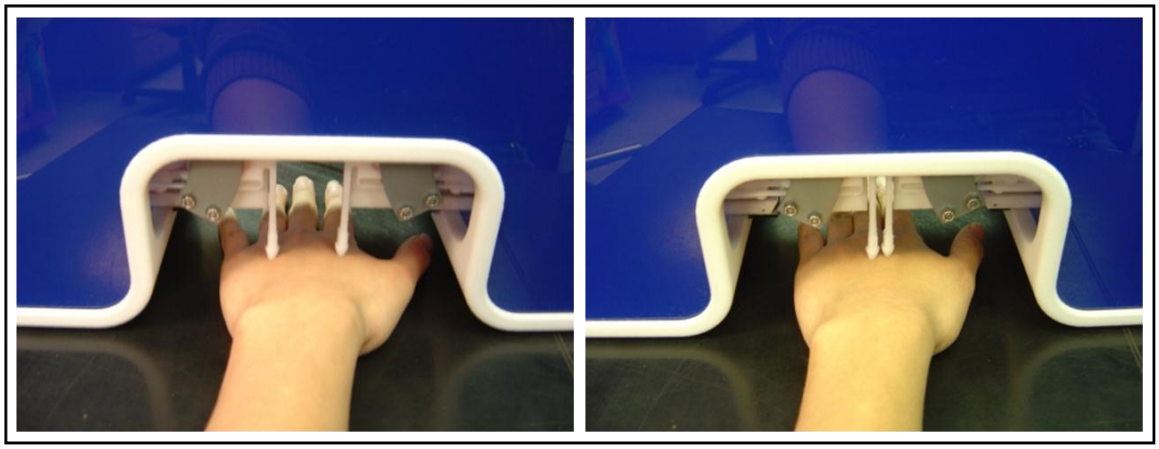

Figure 2.1 Stimulus position on the dorsal surface of the left hand. Probe tips detect the surface of the skin automatically. The stimuli were initially spaced 30 mm apart (left panel of figure) and the inter-stimulus distance was modified on a trial-by-trial basis based on the subject's performance. The minimal inter-stimulus distance possible was 5 mm with 5 mm diameter probe tips (right panel of figure).

A two alternative forced-choice (2AFC) tracking procedure was used to assess a subject's ability to discriminate between the amplitudes of two simultaneously delivered stimuli positioned at near-adjacent skin sites. Each run consisted of 20 trials. At the start of each trial, the two probe tips, 5 mm in diameter, were driven to the skin surface together and automatically stopped after skin detection. The tips were indented 500 um further to ensure good contact with the skin. Two 25 Hz flutter stimuli, identical except for a constant difference in amplitude (standard stimulus: 100 µm vs. test stimulus: 140 µm peak-to-peak amplitude), were delivered. After each trial, the subject was queried as to which skin site received the more intense stimulus. Subjects were instructed to indicate their selection with a switch box with their free hand.

The stimuli were initially spaced 30 mm apart (see Figure 2.1; well above two-point discrimination limen on the hand dorsum; (Tannan, Dennis, and Tommerdahl 2005; Tannan, Dennis, and Tommerdahl 2005; Tannan, Whitsel, and Tommerdahl 2006)), and the inter-

stimulus distance was modified on a trial-by-trial basis based on the subject's performance. During the first 10 trials, a 1 up / 1 down tracking paradigm was used, allowing a single correct answer to cause a 10% reduction in inter-stimulus distance in the subsequent trial. After one inaccurate response, the probe tips were moved 10% further apart. In the last 10 trials, a 2 up / 1 down tracking algorithm was used in which two correct responses were required to decrease the inter-stimulus distance by 10%. The combination of two tracking algorithms in this manner allows the threshold to be determined much faster without compromising the results (Tannan, Dennis, et al. 2007; Tannan, Whitsel, and Tommerdahl 2006).

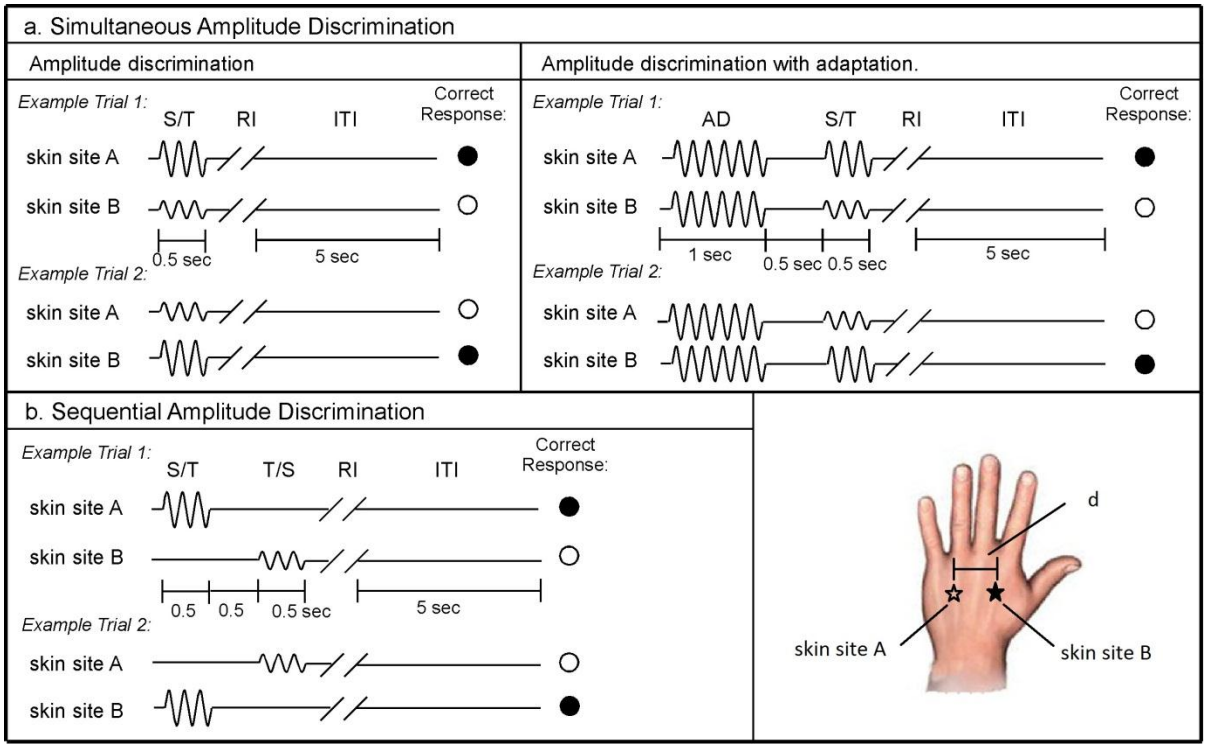

Figure 2.2 Stimulus position and timing diagram of experimental protocols.

The stimulus position and timing diagram of the protocols are shown in Figure 2.2. The task was performed under three conditions: 1) Simultaneous stimulation without adaptation (see Figure. 2.2 a, left panel): in each trial, the standard (S) and test (T) stimuli

were delivered at the same time for 0.5 sec. A 5 sec inter-trial interval (ITI) following the subject response interval (RI) was imposed before onset of the next trial; 2) Simultaneous stimulation with dual-site adaptation (see Figure. 2.2 a, right panel): a pair of adapting stimuli (AD) (identical to the standard stimulus) was delivered first for 1 sec at the same pair of sites as the test and standard stimuli. After a 0.5 sec inter-stimulus interval, the test and standard stimuli were presented simultaneously; 3) Sequential Stimulation (see Figure. 2.2 b, left panel): the standard and test stimuli were presented sequentially with a 0.5 sec inter-stimulus interval. The order and loci of standard and test stimuli were randomized on a trial-by-trial basis. The three run conditions were randomized on a subject-by-subject basis.

Repeated measures analysis of variance (ANOVA) was used to evaluate the difference of the subject's performance under three conditions. Data are presented as means and standard errors (SE). A probability of less than 0.05 was considered statistically significant.

2.4 Results

A subject's ability to discriminate the intensity difference between two vibrotactile stimuli of fixed amplitudes at varying distances between stimulus sites was tracked to approach the inter-probe distance limit at which subjects could not reliably discriminate between the two stimuli. Figure 2.3 is a plot of the averaged response of tracking performance under three different conditions of stimulation. Each condition resulted in a significant change in tracking performance. Comparison of the data obtained in the sequential stimulation condition and the simultaneous stimulation condition demonstrates that the subjects' performance was degraded as the stimuli were moved closer together in the

simultaneous condition, but not in the sequential delivery of stimuli. Note that when the inter-stimulus distance was decreased to approximately 16 mm (near the two-point limen for 25 Hz vibrotactile stimuli on the hand dorsum; (Tannan, Dennis, and Tommerdahl 2005; Tannan, Dennis, and Tommerdahl 2005; Tannan, Whitsel, and Tommerdahl 2006)), discrimination performance became much worse. In contrast, for the sequential condition, subjects were able to correctly discriminate at all inter-stimulus distances, until the separation became 5 mm (minimal inter-stimulus distance possible with 5 mm diameter probe tips). Additionally, subjects' performance under the third condition – the simultaneous stimulation condition with adaptation – shows that pre-exposure to a pair of flutter stimuli (adaptation) at the same locations as the standard and test stimuli improve a subject's discriminative capacity. The data demonstrates a certain degree of consistency across subjects, as variability in the averaged plots of Figure 2.3 is relatively low (note error bars in plots).

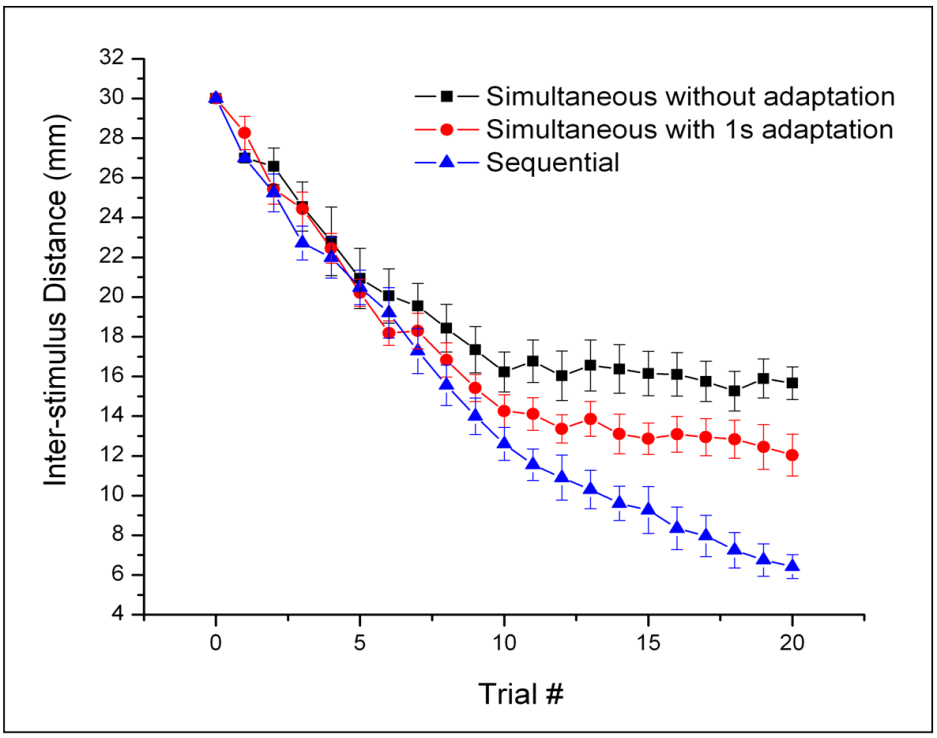

Figure 2.3 Average tracking plots across all subjects under three conditions. The subjects' amplitude discrimination capacity was degraded as the stimuli were moved closer together in the simultaneous condition but not in the sequential condition. Under the third condition, adaptation improves a subjects' discriminative performance under the condition of simultaneous delivery of stimulation.

In order to more directly compare the responses measured under each of the stimulation conditions, the tracking values obtained from the last five trials across all subjects were averaged (Figure 2.4). A significant difference was observed in performance between the simultaneous without adaptation and sequential conditions ($p<0.001$). Additionally, when compared to the simultaneous non-adapting condition, subjects' performance in the simultaneous discrimination task with adaptation was significantly improved by ~20% ($p=0.034$).

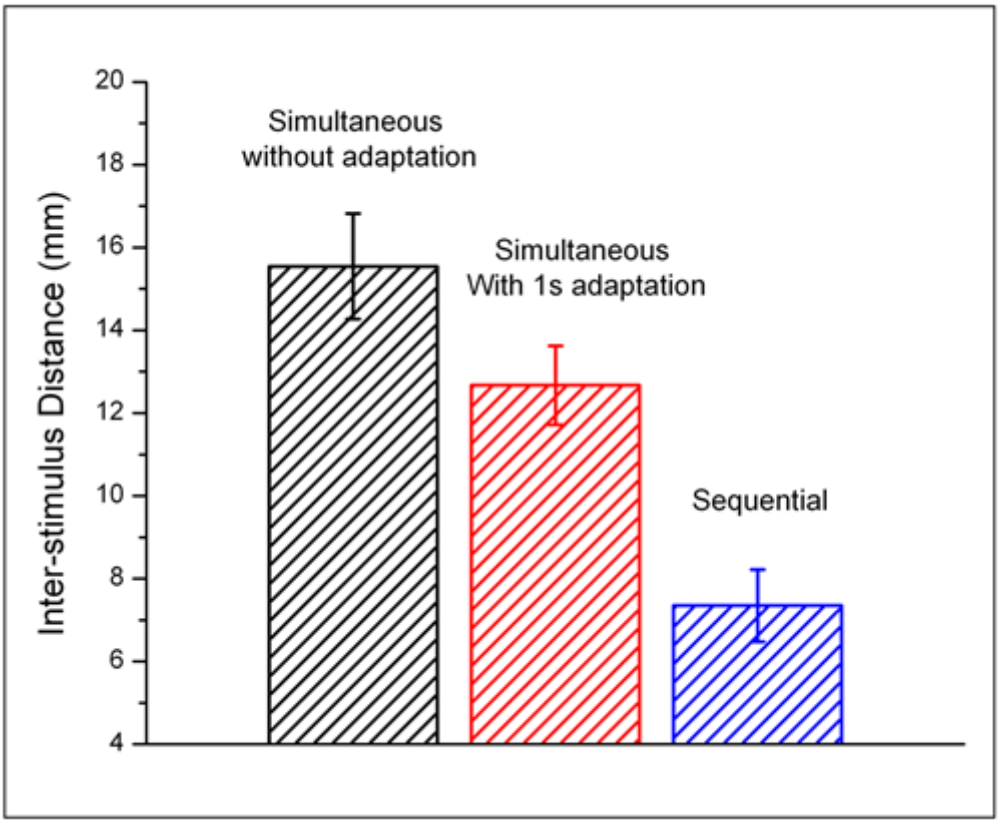

Figure 2.4 Average of the inter-stimulus distances obtained under three conditions. A significant difference was observed in performance between the simultaneous stimulation without adaptation and the sequential conditions ($p<0.001$). Adaptation resulted in a significant improvement (~ 20%) on simultaneous amplitude discrimination at small inter-stimulus distances ($p=0.034$).

2.5 Discussion

In the present study, we investigated the effects of spatial acuity on amplitude discrimination between two flutter stimuli (25 Hz) delivered to the dorsal surface of the hand. The results show that subjects were able to discriminate the amplitude difference between two sequentially delivered stimuli at all inter-stimulus distances from 30 mm to 5 mm (the diameter of the probe tip). When stimuli were presented simultaneously, however, the subjects' ability to discriminate the same amplitude difference was significantly impaired as

the inter-stimulus distance was reduced to 16 mm (near the two-point limen). These results are consistent with a previously published report that demonstrated that amplitude discrimination capacity was significantly worse when inter-stimulus distances were reduced from 30 mm to 5 mm (Tannan, Dennis, et al. 2007). In a task that tracked only a subject's ability to discriminate amplitude differences, Tannan et al found a significant difference in amplitude discrimination capability when the stimuli were delivered simultaneously vs. sequentially at near adjacent skin sites (10 mm or less). Additionally, the results were consistent with the two-point discriminative capacity previously reported for the hand dorsum (16 mm, 17mm, 20mm, and 12mm respectively for four subjects) by Tannan et al (Tannan, Dennis, and Tommerdahl 2005). However, in that study, the inter-subject variability was reported to be much higher (20% vs. 10% of the threshold value), and we suspect that the increased variability in that task was due to the subjective nature of the task. In other words, variability for the findings in this report were lower principally due to the increased objectivity of an amplitude discrimination task that fails due to a decreased spatial discriminative capacity rather than delivering two points to the skin and challenging the subject to only determine whether they felt one or two points.

Sequential and simultaneous test conditions were delivered in order to directly assess the impact that inter-stimulus distance had on a subject's amplitude discrimination capacity. The comparison between sequential and simultaneous stimulus conditions demonstrated that the degradation of amplitude discrimination capacity in the simultaneous stimulus condition was possibly solely due to the subject's inability to discriminate between two points when they were located in near proximity. LaMotte and Mountcastle stated that the ability of a subject to accurately localize a flutter stimulus on the skin is determined by the locus and

clarity of the neuronal population response within the topographically organized SI network (LaMotte and Mountcastle 1975, 1979). When two stimuli are positioned close together on the skin, the activity in the two neuron populations evoked by the two stimuli in the cortex may tend to overlap. As a result, subjects may perceive only one, instead of two distinct sensations. If this is the case, the distance between two stimuli tracked in the simultaneous stimulus condition may be equivalent to the spatial metric that traditional TPD tests were intended to measure.

An important distinction between the protocol used in this study and the traditional two-point discrimination tasks is that the amplitudes of the two stimuli were significantly different, and it is important to consider the spatial extent that larger amplitude stimuli may (or may not) occupy. Simons et al. imaged the optical intrinsic signal of the SI responses evoked by vibrotactile stimulation with different amplitudes in non-human primates (Simons et al. 2007; Simons et al. 2005). They found that as the stimulus amplitude was increased, the activity within the activated region of SI cortex progressively increased although the spatial extent of the activated region remained relatively constant. Rather, with increasing stimulus amplitude and duration, the region surrounding the activated cortical field became less active (or more inhibited), suggesting that more intense and longer duration stimuli would result in more spatially resolved stimuli. Results of the present study appear to be consistent with the findings of Simons and colleagues such that all subjects demonstrated improved discrimination in the simultaneous stimulus condition when the stimulus sites were pre-exposed to 1 s adapting stimulation.

The effects of an adapting stimulus on the perception of subsequent stimuli – particularly the reduction in sensation – have been characterized in some detail (Verrillo and

Gescheider 1977; Delemos and Hollins 1996; Gescheider et al. 1995; Goble and Hollins 1993; Laskin and Spencer 1979; Tommerdahl, Hester, et al. 2005). However, only a relatively small number of studies have assessed the impact that prior exposure to vibrotactile stimuli has on spatial localization or the spatial acuity necessary to discriminate between two points on the skin, and all of these studies demonstrated that adaptation improved spatial acuity (Tannan, Dennis, and Tommerdahl 2005; Tannan, Whitsel, and Tommerdahl 2006; Vierck and Jones 1970; Summers and Chanter 2002). This improvement was originally proposed to be due to the improved spatial clarity between topographically distinct regions of SI cortical activity (LaMotte and Mountcastle 1975, 1979). Two recent reports have examined the effects of stimulus duration-dependent changes on a subject's ability to spatially localize a stimulus. Tannan et al. demonstrated that the performance of neurologically healthy human adults on a spatial localization task undergoes a prominent change with pre-task exposure to an adapting stimulus (Tannan, Whitsel, and Tommerdahl 2006). In that study, it was determined that adaptation with a longer duration (5 sec) vibrotactile stimulus resulted in an approximately 2-fold improvement in spatial localization performance over that achieved with a shorter (0.5 sec) stimulus. It was proposed that this observed improvement in spatial localization was due to the enhanced spatial funneling of the population-level response of contralateral primary somatosensory cortex (SI) – a robust phenomenon that is at least in part due to GABAergic inhibitory neurotransmission (Juliano, Dusart, and Peschanski 1989) and has been demonstrated using comparable stimulus conditions in neuroimaging studies of anesthetized non-human primates (Simons et al. 2007; Simons et al. 2005; Chen et al. 2007). A subsequent report strengthened this argument by demonstrating that neurologically compromised subjects with a known GABAergic

deficiency (adults with autism) showed no such improvement at the same spatial localization task with adaptation (Tommerdahl, Tannan, Cascio, et al. 2007). Thus, there seems to be some evidence that spatial acuity does improve in a stimulus-dependent and GABA-mediated manner that undoubtedly impacts the spatial contrast of cortical activity evoked by vibrotactile stimuli. Changes in the responsivity of neurons have been proposed to underlie the cortical mechanisms for stimulus feature extraction and may be important in the improvements observed in spatial discrimination such as those described above (for review see (Kohn and Whitsel 2002)). This enhancement of discrimination capacity could be due, at least in part, to the moment-to-moment changes that occur in the spatio-temporal patterns of response with repetitive vibrotactile stimulation.

We speculate that the observed improvement of subjects' performance in this study with adaptation is solely due to the effects of adaptation on spatial acuity. It is important to note that in this study, instead of tracking an amplitude difference (as in more commonly performed amplitude discrimination tasks), a constant amplitude difference, which is well above normal subject's amplitude discrimination threshold (Tannan, Dennis, et al. 2007), was maintained while the inter-probe distance was tracked. The subjects' excellent performance under the stimulus condition in which stimuli were delivered sequentially suggests that discriminative capacity (in the simultaneous stimulation condition) was predominantly impacted by the spatial parameters imposed by the inter-stimulus distance. As a result, when two stimuli were delivered simultaneously and in near-proximity, the effects of pre-exposure to dual-site adapting stimuli would be to facilitate the discriminative aspect affected by spatial acuity, but not necessarily facilitate what would normally be an easy amplitude discriminative task. Thus, any adaptive effects on the amplitude discriminative

task – which have been reported in several studies (Tannan, Simons, et al. 2007; Gescheider et al. 1995; Goble and Hollins 1993; Delemos and Hollins 1996) – could most likely be regarded as having little impact on the results in this study.

CHAPTER 3

IMPACT OF NON-NOXIOUS HEAT ON TACTILE INFORMATION PROCESSING

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3.1 Abstract

A significant number of studies that evaluated tactile-pain interactions employed heat to evoke nociceptive responses. However, relatively few studies have examined the effects of non-noxious thermal stimulation on tactile discriminative capacity. In this study, the impact that non-noxious heat had on three features of tactile information processing capacity were evaluated: vibrotactile threshold, amplitude discriminative capacity and adaptation. It was found that warming the skin made a significant improvement on a subject's ability to detect a vibrotactile stimulus, and although the subjects' capacities for discriminating between two amplitudes of vibrotactile stimulation did not change with skin heating, the impact that adapting or conditioning stimulation normally had on amplitude discrimination capacity was significantly attenuated by the change in temperature. These results suggested that although the improvements in tactile sensitivity that were observed could have been a result of enhanced peripheral activity, the changes in measures that reflect a decrease in the sensitization to repetitive stimulation are most likely centrally mediated. The authors

speculate that these centrally mediated changes could be a reflection of a change in the balance of cortical excitation and inhibition.

3.2 Introduction

Studies of human somatosensory perceptual capabilities not only have demonstrated that clear and strong interactions occur between temperature and touch, but have provided evidence suggesting that the responsible neural interaction occurs at a relatively early stage of the somatosensory projection pathways. As examples, (1) noxious thermal stimulation applied within the same dermatome (but not at a more remote skin site) elevates the threshold for detection of cutaneous vibrotactile stimulation regardless of which mechanoreceptive channel is activated by the mechanical stimulus (Apkarian, Stea, and Bolanowski 1994; Bolanowski et al. 2000; Bolanowski et al. 2001), (2) experimental inflammatory pain and the pain that results from topical capsaicin application impairs tactile discriminative abilities in normal subjects (Kauppila et al. 1998), (3) patients with persistent musculoskeletal pain exhibit an elevated threshold for detection of cutaneous flutter stimulation as well as impaired ability to discriminate vibrotactile stimulus frequency (Hollins et al. 1996; Hollins and Sigurdsson 1998), and (4) cutaneous vibration (especially at frequencies >100Hz) significantly suppresses both clinical and experimental pain (Pertovaara 1979; Ekblom and Hansson 1982, 1985; Lundeberg 1984, 1984, 1984, 1984, 1984; Lundeberg, Nordemar, and Ottoson 1984; Pantaleo, Duranti, and Bellini 1986; Sherer et al. 1986). Additionally, neurophysiological observations from non-human primates have provided evidence for interactions between the responses evoked in SI cortex to both noxious skin heating and skin flutter stimulation (Tommerdahl, Delemos, et al. 1996; Tommerdahl et al. 1998) –

interactions fully consistent with the published human psychophysical demonstrations of prominent interactions between the sensory experiences of touch and heat-evoked pain.

However, although there have been numerous studies that evaluated tactile-pain interactions that utilized heat to evoke nociceptive response, relatively fewer studies have examined the effects of non-noxious thermal stimulation on touch. Tracing back to 1846, E.H. Weber (Weber 1846) noted that a cold coin (-4 to -7 ℃) resting on the forehead feels heavier than a warm coin (38 to 39 ℃), implying an effect of non-noxious temperature on the touch modality. Since then, a number of studies have reported that changes of tactile sensitivity (ex. tactile spatial acuity, punctuate pressure sensitivity, and vibrotactile sensitivity) take place with warming and cooling of the skin (Green, Lederman, and Stevens 1979; Stevens, Green, and Krimsley 1977; Bolanowski and Verrillo 1982; Verrillo and Bolanowski 1986; Gescheider et al. 1997). For example, Green (Green, Lederman, and Stevens 1979) examined the effect of skin temperature on the perception of roughness. The results demonstrated that warming above normal skin temperature either *enhances* the perception of roughness for smooth surfaces or leaves it unchanged for rough surfaces. However, Stevens and colleagues (Stevens, Green, and Krimsley 1977) found that a small but possibly insignificant *loss* of sensitivity for detection of punctuate pressure appeared at skin temperatures of 40℃ and 43℃. Other observations on the impact of elevated skin temperature on vibrotactile sensitivity also appear to be inconsistent. Weitz (Weitz, 1941) and Green (Green et al., 1977) reported that warming the skin a few degrees above normal (36 - 37 °C) resulted in an increase of sensitivity to high-frequency vibration (>80 Hz). However, Verrillo et al (Verrillo and Bolanowski 1986) reported no changes of the sensitivity on the forearm and thenar eminence as the skin temperature was increased from 30° to 40°C, while Bolanowski showed

only a slightly elevated threshold on detecting 25Hz vibrotactile stimulation (Bolanowski and Verrillo 1982).

The goal of this study was to examine the impact that non-noxious heat has on three features of tactile information processing capacity: vibrotactile threshold detection, amplitude discriminative capacity and adaptation. It was found that warming the skin made a significant improvement on threshold detection, and although the subjects' capacities for discriminating between two amplitudes of vibrotactile stimulation did not change with skin heating, the impact that adapting or conditioning stimulation normally has on amplitude discrimination was significantly attenuated by the change in temperature.

3.3 Methods

Ten subjects participated in this study (21–28 years in age). They were naïve both to the study design and issue under investigation. The subject group consisted of 4 males and 6 females, all right-hand dominant. The study was performed in accordance with the Declaration of Helsinki, all subjects gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board. Four separate protocols were employed to measure the effects of non-noxious thermal stimulation on vibrotactile detection, amplitude discrimination, and the impact of vibrotactile adaptation on tactile discrimination capacity. During an experimental session, the subject was seated comfortably in a chair with the right arm resting on an acrylic hand-arm rest attached to a portable dual-site vibrotactile stimulator (CM-1; for full technical description see (Tannan, Dennis, et al. 2007); for exemplary use of the device, see (Tommerdahl, Tannan, Cascio, et al. 2007; Tommerdahl et al. 2008; Tommerdahl, Tannan, Zachek, et al. 2007;

Folger et al. 2008; Francisco et al. 2008; Zhang et al. 2008; Tannan, Simons, et al. 2007). Two holes (10 mm diameter each, spaced 35 mm apart) were positioned on the hand-arm rest to allow the stimulator tips to make contact with digits 2 and 3 of the subject's right hand (right panel in Figure 3.1). A temperature-controlled metal hand plate was fabricated to attach on the front top end of the acrylic hand-armrest for this study. This metal hand plate was composed of 2.5 mm thick aluminum sheet (alloy 6061-T6), cut to a rectangular shape 150×300 mm in size. The sheet was bent to the same shape as the original hand-armrest, and two 10mm holes were positioned for D2 and D3 stimulation (Figure 3.1). Two 15W flexible heater pads with a thermocouple between them were embedded in the temperature-controlled plate. A fuzzy-logic P-I-D auto-tuning temperature controller (McMaster-Carr #7981K82) was used to externally monitor and control the temperature. The auto-tuning controller automatically optimizes the P, I, and D control gains to tune the system to achieve the fastest possible response with minimum temperature overshoot. The desired temperature set point was entered prior to each experimental run and held constant for the duration of the run.

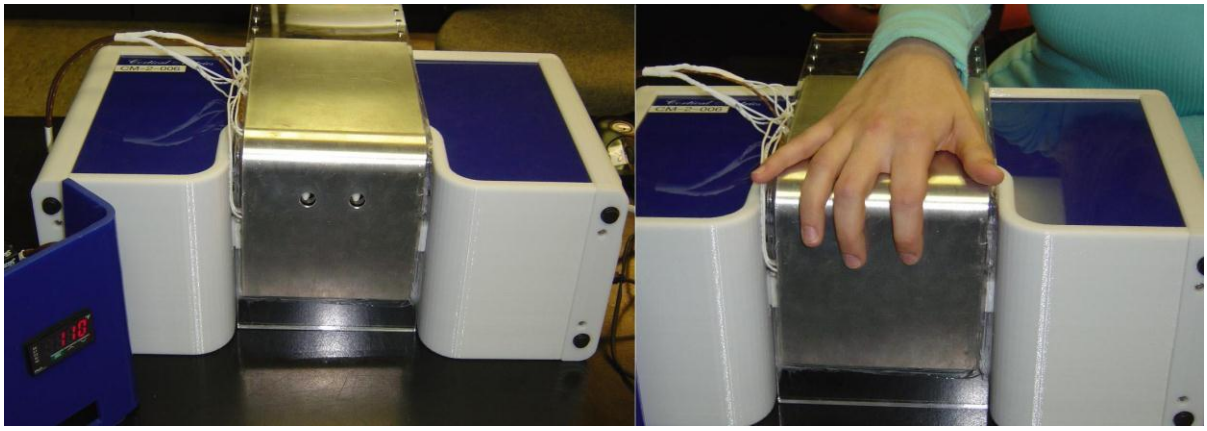

Figure 3.1 Images of the vibrotactile stimulator with a temperature-controlled metal hand plate attached. Two holes (10 mm diameter each spaced 35 mm apart) were positioned to allow the stimulator tips to make contact with subject's digits. During an experimental session, the subject was seated comfortably in a chair with the right arm resting on the metal hand plate. Index and middle finger were positioned for D2 and D3 stimulation.

During each test, two probe tips (5 mm diameter) were positioned on the glabrous pads of digits 2 and 3 of the right hand. D2 and D3 were chosen as the test sites for two reasons: (1) to allow the convenience of access and comfort for the subject, thus maximizing the test's potential in clinical applications, and (2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of cortex in primates. Visual cueing was provided with a computer monitor during the experimental runs. Specifically, an on-screen light panel indicated to the subject when the stimulus was on and when the subject was to respond. The subject was not given performance feedback or knowledge of the results during data acquisition until all sessions were completed. At the start of each run, the two probe tips were driven towards the skin until each tip registered a force of 0.1 g, as determined by a closed-loop algorithm in the CM-1 stimulator feedback system. The tips were then further indented into the skin by 500 μm to ensure good contact with the skin. All sinusoidal vertical skin displacements were delivered by the CM-1 stimulator. An audiometer was used to make certain that no auditory cues were emitted from the stimulator during delivery of the range of stimuli used in this study. Practice trials allowed the subject to familiarize with the tests, and correct responses on 5 consecutive trials were required before commencing with each test. During the experimental session, the room temperature was controlled around 25 ℃. The subject completed all four tests (described below) first at room temperature, then after a 10-minute break, they repeated all four tests under the condition with increased hand rest temperature: 40.5 °C or 43 °C. In each condition, the order of the four tasks was randomized across all of the subjects.

Detection threshold - In order to measure the subject's vibrotactile detection threshold, a 20-trial Two-Alternative Forced Choice (2AFC) tracking protocol was employed

(for recent description with this experimental setup, see (Francisco et al. 2008)). Figure 3.2a shows the schematic of the protocol. During each trial of the experimental run, a 25 Hz vibrotactile test stimulus was delivered to either D2 or D3 (the stimulus location was randomly selected on a trial-by-trial basis). Stimulus duration was 0.5 sec, followed by subject response (subject was queried to select the skin site that received the stimulus) and a 5 sec delay before onset of the next trial. At the beginning of the experimental run, the test stimulus amplitude was 15 μm (all vibrotactile stimulus amplitudes reported in this study are peak-to-peak). In the initial 10 trials, the test amplitude was modified based on the subject's response in the preceding trial, accomplished using a 1-up/1-down algorithm (the amplitude was decreased if the subject's response in the preceding trial was correct; it was increased if the response was incorrect). After the initial 10 trials were completed, the test amplitude was modified using a 2-up/1-down algorithm — in the remaining 10 trials two-correct/one-incorrect subject response(s) resulted in a decrement/increment, respectively, in the amplitude of the stimulus. This approach was selected because it enabled rapid determination ("tracking") of each subject's minimally detectable amplitude of vibrotactile stimulation (Folger et al. 2008; Francisco et al. 2008; Tannan, Dennis, et al. 2007; Zhang et al. 2008). The step size was held constant at 1 μm throughout the experimental run.

Amplitude discrimination - Each subject's amplitude discrimination capacity was observed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies (Folger et al. 2008; Francisco et al. 2008; Tannan, Dennis, and Tommerdahl 2005; Tannan, Dennis, et al. 2007; Tannan, Simons, et al. 2007; Tannan, Whitsel, and Tommerdahl 2006; Tommerdahl, Tannan, Cascio, et al. 2007; Zhang et al. 2008). During the 20-trial experimental run, a vibrotactile test stimulus (25 Hz, amplitude

between 105 and 200 μm) was delivered to one digit pad at the same time that a standard stimulus (25 Hz, amplitude fixed at 100 μm) was applied to the other digit pad (Figure 3.2c, left panel). The loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. At the beginning of the experimental run, the test amplitude was 200 μm and the standard amplitude was 100 μm. The difference between the amplitudes of the test and standard stimuli was adjusted on the basis of the subject's response in the preceding trial, such that the difference was decreased/increased after a correct/incorrect response, respectively. The same tracking algorithm as that described for the tactile detection threshold protocol was employed, and the step size was held constant at 10 μm throughout the experimental run.

Amplitude discrimination with adaptation - In order to measure the gain effects that conditioning stimuli have on subsequent stimuli, the previously described amplitude discrimination protocol was modified such that delivery of the test and standard stimuli was preceded by a single conditioning stimulus to one of the two stimulus sites (Figure 3.2c, right panel). The result of such a protocol modification is that the amplitude discrimination difference limen (DL) is typically significantly elevated (Folger et al. 2008; Tannan, Simons, et al. 2007; Zhang et al. 2008). Specifically, a 25 Hz 200 μm conditioning stimulus was delivered 1 sec prior to the presentation of the test and standard stimuli. When the conditioning stimulus is delivered to the same site as the test stimulus, the effect of reducing the perceived intensity in this condition can be quantified by comparison of the DLs obtained in the adapted vs. non-adapted conditions. The duration of the conditioning stimulus was 1 sec, which was followed by a 1 sec delay before onset of the simultaneous delivery of the test and standard stimuli. The amplitude discrimination tracking algorithm used in the previously

described protocol was used to track the subject's ability to determine the most intense stimulus (i.e., the subject's DL was determined).

Dynamic tracking of adaptation - A novel protocol termed “dynamic tracking” was implemented to further characterize the effects of adaptation on amplitude discrimination (Figure 3.2b). At the start of each experimental run, two vibrotactile stimuli (25 Hz; initially identical in amplitude at 300 μm) were delivered simultaneously to D2 and D3. Four conditions of initial constant stimulus duration (n sec) were employed, in separate experimental runs: 0, 1.5, 2, and 3 sec. After the initial constant stimulus period, the amplitudes of both stimuli were dynamically altered such that the amplitude of one stimulus was increased and the amplitude of the other stimulus was decreased, in steps of 25 μm/sec. The subject was instructed to indicate the location at which the most intense stimulus was delivered as soon as the two stimuli felt distinctly different in intensity. For each experimental run, the difference limen (DL) was measured as the actual difference between the two test amplitudes at the time of subject response (msec).

D'Agostino-Pearson test (α=0.05) was performed to test whether the data points under each condition were sampled from a Gaussian distribution. Repeated-measures analysis of variance (ANOVA) was used to evaluate the difference of the subject's performance under different conditions. Data are presented as means and standard errors (SE). A probability of less than 0.05 was considered statistically significant.

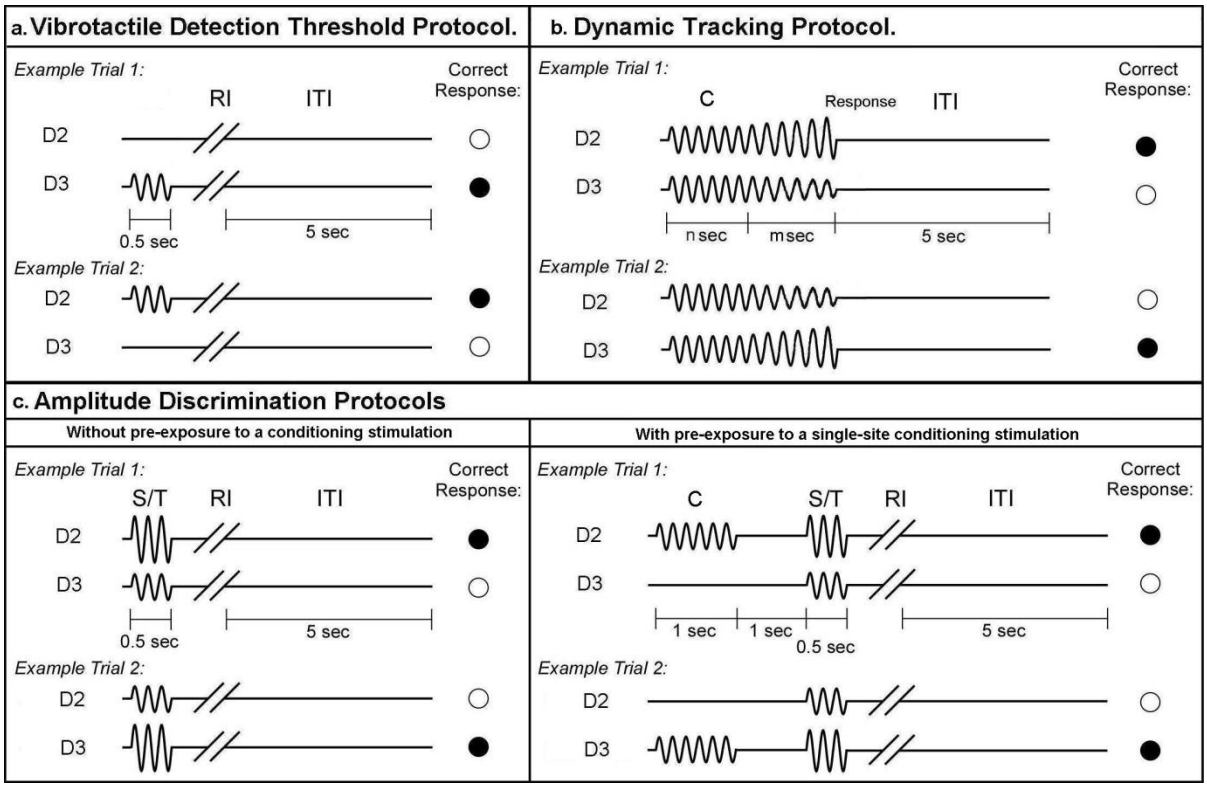

Figure 3.2 Schematics of the experimental protocols used in this study.

3.4 Results

In order to assess the impact that non-noxious heat has on tactile information processing capacity, comparisons of subject performance were obtained for different conditions of thermal stimulation. Protocols were employed to assess the impact of non-noxious thermal stimulation on subjects' capacities for vibrotactile detection (at room temperature, 40.5°C, and 43°C), amplitude discrimination (at room temperature and 43°C), and the effect of vibrotactile adaptation on tactile discrimination capacity (at room temperature and 43°C).

Vibrotactile thresholds decrease with increasing temperature. A Two-Alternative Forced Choice (2AFC) protocol was used to determine a subject's vibrotactile detection threshold (stimuli delivered at a frequency of 25Hz to one of two stimulus sites and subject

reports the site of stimulus detection; previously reported in Francisco et al. 2008; also see description in Methods) for each of the three temperatures. In Figure 3.3, Panel A summarizes the group-averaged detection thresholds obtained under the three thermal conditions. Specifically, at room temperature the group-averaged vibrotactile detetion threshold on fingertip was 7.28 ± 0.84um (mean±SE), which is consistant with the detection thresholds (~7um) reported by Mountcastle and colleagues (Mountcastle, LaMotte, and Carli 1972). While temperature was increased, subjects were consistently able to detect stimuli at amplitudes of 5.98 ± 0.57um (40.5℃) and 4.83 ± 0.93um (43℃). Note that detection thresholds decrease with increasing temperature. Thus, concurrent non-noxious thermal stimulation results in an *improvement* of vibrotactile sensitivity. Specifically, at 40.5℃, the data suggest an improvement in sensitivity (or a decrease in detection threshold) when compared to the room temperature condition, although this difference was not statistically significant ($p = 0.18$). However, the improved sensitivity that was suggested with increased temperature in the 40.5℃ condition was much more pronounced for the 43℃ condition, at which the detection threshold was significantly lower than that at the room temperature condition ($p = 0.047$). In order to determine if this trend was consistent within subjects, the data were normalized to the room temp condition, shown in Figure 3.3 Panel B. The normalized plot confirms that subjects' detection thresholds were reduced as the thermal stimulation was increased, and strongly suggests improved detection performance with increasing temperature in the non-noxious thermal temperature range. Specifically, performance was improved over that at room temperature by ~21% at 40.5℃, and by ~42% at 43℃.

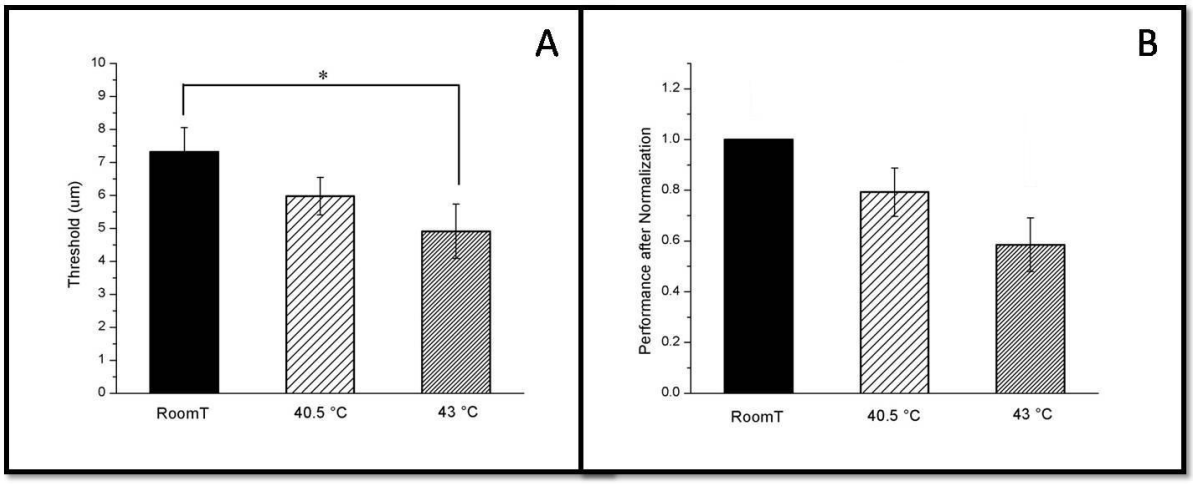

Figure 3.3 Comparison of vibrotactile detection thresholds obtained under three different temperature conditions (room temperature, 40.5℃, and 43℃). A) The group-averaged detection threshold at three skin temperatures. B) Detection thresholds normalized on a subject by subject basis to the room temperature condition. The plots show that increase skin temperature to 43℃ significantly reduced the subject's tactile detection threshold ($p = 0.047$).

Increasing temperature had little impact on a subject's vibrotactile amplitude discriminative capacity, but did attenuate the effects normally caused by pre-exposure to a conditioning stimulus on that assessment. A second 2AFC tracking protocol was employed to determine subjects' capacities to discriminate between the amplitudes of two simultaneously delivered vibrotactile stimuli with or without a preceding conditioning stimulus delivered to one of the stimulus sites (see Methods). Figure 3.4 summarizes the averaged across-subject performance for the results obtained with the two amplitude discrimination protocols (with or without single-site adaptation) at room temperature and at 43℃. The results demonstrate that, in the absence of pre-exposure to a conditioning stimulus, subjects were able to discriminate between a 100 μm and a 123 μm stimulus (DL = 23 μm) equally well under both temperature conditions (as shown on the left hand side of Figure 3.4). Previous reports have shown that, in normal healthy control conditions, amplitude discrimination capacity is significantly impacted with the delivery of a conditioning stimulus

to one of the two stimulus sites prior to the amplitude discrimination task (Folger et al. 2008; Tannan, Simons, et al. 2007). In this study, the observed subjects' performance is in a manner consistent with previous studies. Specifically, subjects' capacities for amplitude discrimination was significantly impaired with pre-exposure to a conditioning stimulus under both temperature conditions ($p < 0.01$ at room temperature; $p = 0.032$ at 43℃). One interpretation of this impairment is that a 1 sec conditioning stimulus reduces the perceived intensity of the subsequent test stimulus to the extent that a stimulus with amplitude of approximately 160 µm (at room temperature) / 140 µm (at 43℃) was perceived nearly the same in intensity as the 100 µm stimulus. Note that the average post-adaptation DL at room temperature increased to about 160% above the value obtained with the non-adaptation protocol, yet the averaged post-adaptation DL at 43℃ was only about 73% above the non-adaptation values. Thus, the temperature increase resulted in a significant reduction in the impairment of subjects' amplitude discrimination capacity due to adaptation ($p = 0.043$) (as shown in Figure 3.4 on right side). In summary, as temperature was increased, the impact of the conditioning stimulus was lessened, and subjects subsequently performed better at the post-adaptation amplitude discrimination task relative to their performance at room temperature.

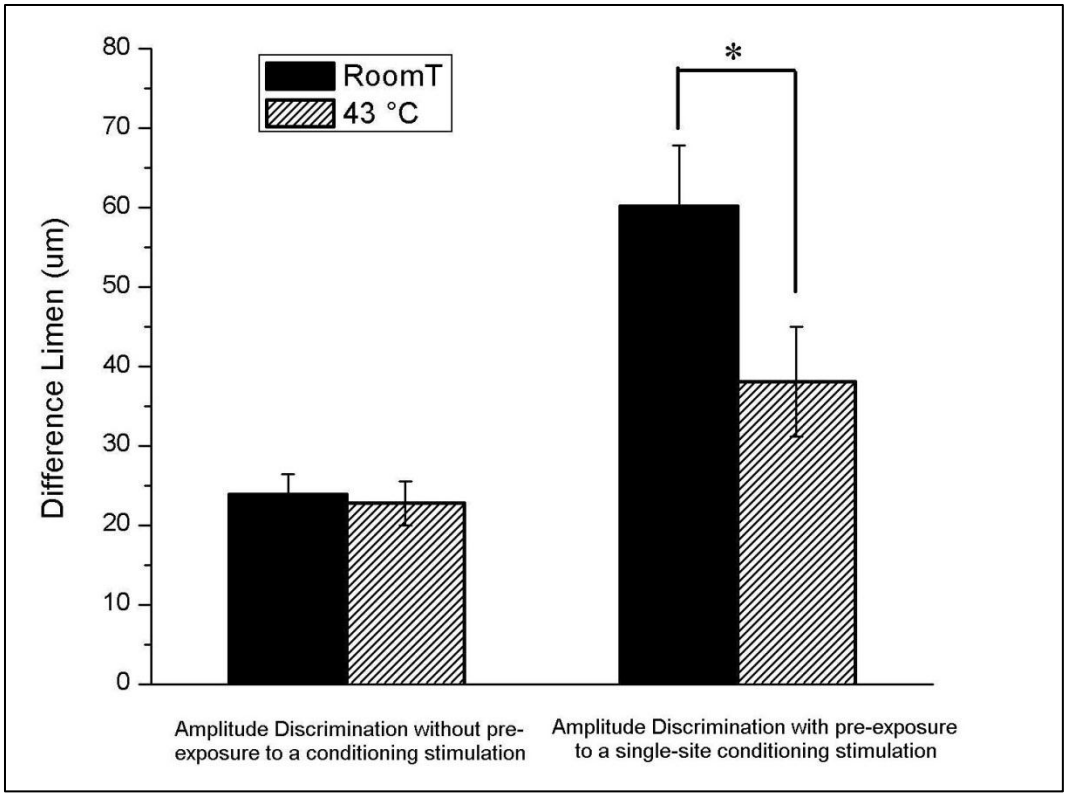

Figure 3.4 Comparison of difference limen obtained with two amplitude discrimination protocols (with/without pre-exposure to single-site conditioning stimuli) at room temperature and at 43℃. In the absence of conditioning stimuli, increasing skin temperature had little impact on a subject's amplitude discrimination capacity. However, the impairment of amplitude discrimination capacity due to conditioning stimulation was significantly reduced when the skin temperature was increased from room temp to 43°C.

Discriminative capacity, normally impacted in a stimulus duration dependent manner, is less impacted in the presence of a 43^{o}C thermal stimulus. To further investigate the effects of thermal non-noxious stimulation on adaptation, a 2AFC dynamic amplitude discrimination protocol (see Methods) was employed which is able to effectively compare the degree to which a subject adapts to simultaneously delivered dual-site vibrotactile stimuli at different durations of conditioning stimulation. Four conditions of initial constant stimulus duration were employed, in separate experimental trials: 0, 1.5, 2 and 3 sec. After the initial constant stimulus period, subjects performed an amplitude

discrimination task on stimuli which diverged in amplitude at the rate of 25 μm/s (i.e., one stimulus amplitude became larger and one became smaller; see Methods for description). Figure 3.5 summarizes the averaged across-subject performance with dual-site adaptation at the four different durations of conditioning stimulation at room temperature and 43℃. The results show that, at room temperature, increasing the duration of the conditioning stimuli delivered to both sites of skin stimulation led to an improvement of a subject's capacity to detect the difference in amplitude between the two stimuli. For example, after pre-exposure to 1.5s, 2s or 3 s conditioning stimulus, subjects were, on average, able to attain a DL (182um, 139um, or 82 μm) that was ~75%, ~57%, or ~34%of the DL (242 μm) obtained without adaptation (under all the conditions $p < 0.01$). However, when the skin was heated to 43℃, the improvement in amplitude discrimination previously observed with increasing conditioning stimulus durations was significantly attenuated. Specifically, after pre-exposure to 1.5s, 2s or 3s conditioning stimulus, subjects were able to attain a DL (203um, 193um, or 184um) that was ~85%, ~81%, or ~77% of the DL (238um) obtained without adaptation. Note, at the 2 s and 3 s conditioning stimulation durations, the improvement in amplitude discrimination obtained at room temperature (57% and 34%) were significantly different from the 43℃ condition (81% and 77%): 2 s adaptation: $p = 0.024$; 3 s adaptation: $p < 0.01$.

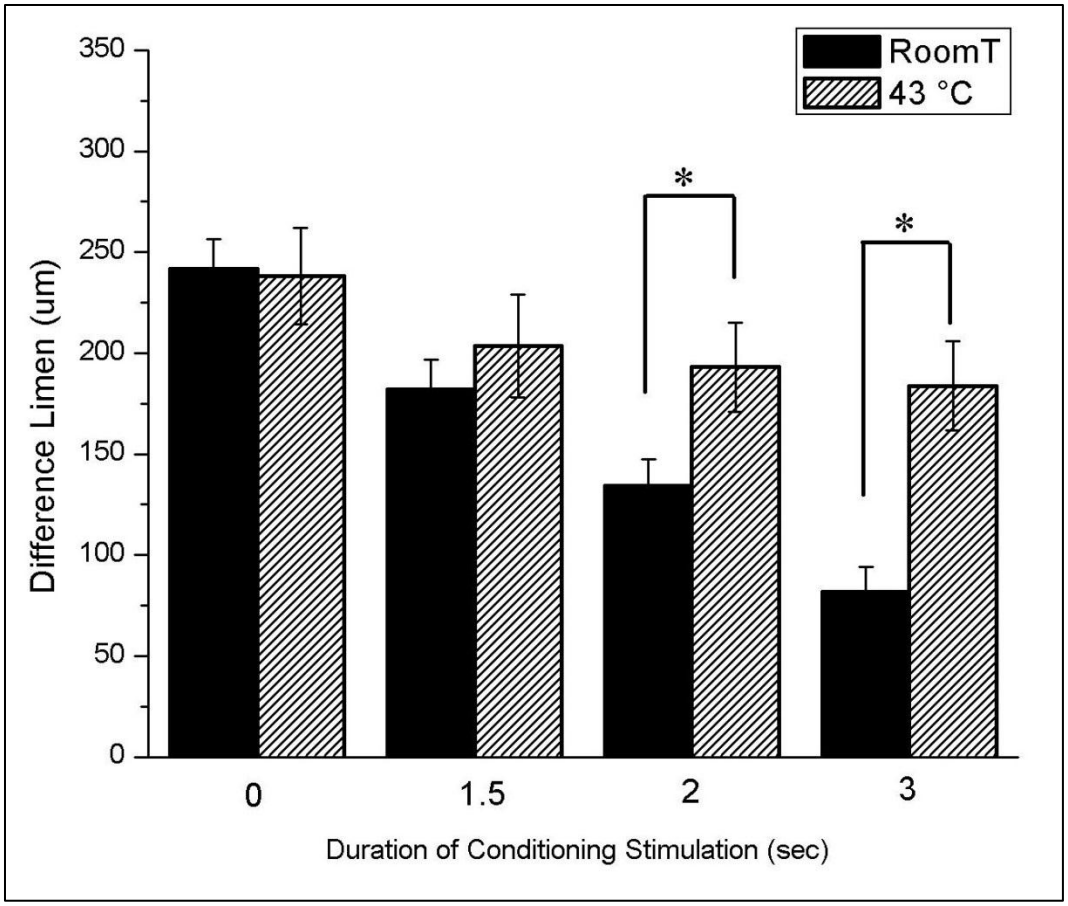

Figure 3.5 Comparison of effects of temperature on dual-site conditioning at four different durations. At room temperature, increasing the duration of the conditioning stimulation led to an improvement of amplitude discrimination performance. However, this improvement was significantly reduced at 43℃.

3.5 Discussion

In the present study, we investigated the effects of non-noxious heat on subjects' tactile information processing capacities. The results strongly suggest that concurrent non-noxious thermal stimulation (43℃) enhances some aspects of vibrotactile sensitivity (e.g., detection threshold). It was also found that although the same increase in temperature had no effect on the subjects' performance on vibrotactile amplitude discriminative capacity, the non-noxious heat significantly reduced the impact that pre-exposure to vibrotactile stimuli (i.e., a conditioning stimulus) had on amplitude discriminative capacity.

In this study, the effect of temperature (within the non-noxious temperature range) on the threshold for detection of cutaneous vibrotactile stimulation was studied. The data demonstrated a significant improvement in vibrotactile sensitivity (i.e., a decrease in detection threshold) as the temperature of the forearm rest was increased from room temperature to 43°C. Since the 19th century, the effects of skin temperature on tactile sensitivity have been examined across a wide spectrum of temperatures, both noxious and non-noxious. Although a number of studies have demonstrated that noxious skin heating results in a robust elevation of the vibrotactile threshold (Apkarian, Stea, and Bolanowski 1994; Bolanowski et al. 2001; Bolanowski et al. 2000), results of the impact of non-noxious skin heating on vibrotactile sensitivity have been much less consistent (Bolanowski and Verrillo 1982; Gescheider et al. 1997; Green, Lederman, and Stevens 1979; Verrillo and Bolanowski 1986; Bolanowski et al. 1988). A number of possible factors may influence the impact of temperature on threshold detection and account for the diverse results found in previous studies. For example, many studies differed in the region of the body stimulated. In the present study, subjects' fingertips were stimulated with 25Hz vibrotactile stimulation, and a significant decrease in threshold was found as the temperature was increased from room temperature to 43°C. However, in a number of previous studies in which subjects' forearm and thenar eminence were utilized as stimulus sites, conflicting results were reported. For example, Bolanowski and Verrillo investigated vibrotactile threshold-frequency characteristics at different skin temperatures and found that increasing thenar eminence temperature from 25°C to 43°C slightly elevated subjects' vibrotactile threshold at low frequency (<100Hz). However in another study, the same authors reported that there was no change in threshold on the forearm as the temperature was increased from 30°C to 40°C. Additionally, Stevens found that warming had little or no

effect on touch magnitude perception on the forehead but it did result in a significant effect on the perceived intensity of the stimulus on the forearm (Stevens and Green 1978). In addition to different stimulus sites, the inconsistent results previously observed could also be partially due to the fact that skin temperature was controlled in different manners in the aforementioned studies. For example, in a number of studies (Bolanowski et al. 1988; Bolanowski and Verrillo 1982; Verrillo and Bolanowski 1986) skin surface temperature of only the surround of the stimulus contactor was controlled, and thus, only the temperature of a small skin area receiving the mechanical stimulation was controlled. In the present study, the temperature of subjects' distal forearm was elevated and as a result, a much larger skin area experienced an elevated temperature than that observed in any of the prior studies. As it is well known that spatial summation plays a significant role in temperature sense (Stevens, Marks, and Simonson 1974; Stevens and Banks 1971), the area of skin that is warmed could obviously play a significant role in the results.

The impact of warming on the adaptation paradigms studied in this report has not been previously reported. In fact, to the authors' knowledge, there have been no studies to date that have assessed the impact of changing temperature – either in the noxious or non-noxious range – on the impact of changes in perception that normally result from repetitive vibrotactile stimulation. There have been a number of reports on the sensitivity of adaptation on a number of aspects of somatosensory perception. Several studies reported that when the conditioning stimulus is increased in duration or amplitude, the perceived intensity evoked by subsequent test stimuli is reduced (Gescheider, Frisina, and Verrillo 1979; Hollins et al. 1990; Verrillo and Gescheider 1977). More recently, Tannan et al demonstrated that increasing the stimulus duration at one of two stimulus sites prior to simultaneous delivery of two stimuli

systematically impacted subjects' amplitude discrimination capacities (Tannan, Simons, et al. 2007). The results from that study demonstrated an increase in stimulus duration is proportional to a decrease in perceived intensity, thus yielding a measure of how much a subject adapts to different durations of vibrotactile stimuli in the range of 0.2 to 5 seconds, and these measures are paralleled in animal studies in which observations of central and peripheral responses to repetitive mechanical stimulation were obtained. Neurophysiological studies have demonstrated that the effects of reduced intensity due to adapting stimulation are possibly attributable to a reduction in the responsivity of central neurons or in synaptic processes associated with the central neurons after prolonged or repetitive stimulation. More specifically, O'Mara and colleagues (O'Mara, Rowe, and Tarvin 1988) found that extended exposure to a vibratory stimulus produced substantial reductions in the responsivity of neurons in the cuneate nucleus, but not in the peripheral afferents. Lee and Whitsel (Lee and Whitsel 1992) reported that repetitive brushing stimuli frequently lead individual SI neurons and neuron groups to modify their response to the repetitive afferent drive. Additionally, Lee and Whitsel (Lee, Whitsel, and Tommerdahl 1992) found that the majority (~58%) of the SI neurons sampled showed a decreased response to repetitive stimulation (3-5 Hz) of their receptive fields. In that report, it was proposed that the glutamate-mediated excitatory effects on NMDAR are to a large extent responsible for the appreciable capacities of cortical neurons to modify their physiological properties with repetitive sensory experience.

In current study, the amplitude discrimination with single-site adaptation protocol and the dynamic tracking with dual-site adaptation protocol measured two distinct effects of adaptation. At room temperature, during Amplitude Discrimination test, a 1 sec conditioning stimulus delivered to one of the stimulus sites reduces the perceived intensity of the

subsequent test stimulus and significantly IMPAIRED the subjects' capacities for amplitude discrimination. However, in the dynamic tracking test, different durations of conditioning stimulation (1.5s, 2s, or 3s) delivered to both sites of skin stimulation led to significant IMPROVEMENT of a subject's capacity to detect the difference in amplitude between the two stimuli. In terms of the difference in the magnitude of influence of non-noxious heat on the impact of the conditioning stimulus in the two tasks, the effect of single-site adaptation on amplitude discrimination appears to be more sensitive to temperature change when compared to the effect of dual-site adaptation on dynamic tracking. The noticeable difference in the difference limen between two tasks could be explained with a couple of possibilities. (1) Two standard stimulus amplitudes (100um vs. 300um) were used. According to Weber's law, the subjects' capability to discriminate differences in vibrotactile amplitude changes systematically with increasing stimulus magnitude. (2) Several studies have reported that the psychophysical measurement methods had a significant influence on vibrotactile thresholds (Morioka and Griffin 2002; Maeda and Griffin 1995). For example, Morioka and colleagues found that with intermittent stimulation the vibrotactile thresholds tended to be lower than with continuous stimulation. Therefore, during dynamic tracking test the continuous stimulation with ascending amplitude might result in the higher difference limen than which recorded in the amplitude discrimination test with intermittent stimulation.

One of the more interesting questions that this study poses is for what reason is the impact of adaptation significantly reduced in the presence of warmth? Mechanistically, it is most likely a change in the balance of excitation and inhibition that is prevalent among cortical neurons. The changes that occur with warmth are reminiscent of the changes in tactile sensibilities that are observed in autism: subjects with autism typically have increased

sensitivity to a number of stimulus modalities (Kanner 1943; O'Riordan and Passetti 2006), are not significantly different from controls in amplitude discriminative capacity (Tannan et al. 2008), but show a reduced response to repetitive stimulation – or less of an adaptive response(Tannan et al. 2008; Tommerdahl, Tannan, Cascio, et al. 2007). In the case of autism, the hyper-excitability has been speculated to be the result of inhibitory deficient circuitry, possibly linked to genetic disparity in GAD (Glutamic acid decarboxylase) which is responsible for normal conversion of glutamate to GABA (Gamma-aminobutyric acid). In the case of this study, could warmth simply be making either peripheral and/or central neurons more hypersensitive to flutter vibration? A series of studies (Bolanowski and Verrillo 1982; Verrillo and Bolanowski 1986; Green 1977) demonstrated that the pacinian corpuscle (PC) channel is strongly affected by skin temperature. Since the PC channel is predominantly sensitive to high-frequency (>80Hz) vibrotactile stimulation, its characteristic change with temperature is not consistent with the findings of this report, as the observations in this study were obtained with delivery of low frequency (25Hz) vibrotactile stimuli. In similar fashion, the touch gate is activated by the presence of thermally induced pain that increases tactile thresholds (Apkarian, Stea, and Bolanowski 1994), yet in the current experiment, non-noxious thermal stimulation was employed. Thus, the observation that warming the skin within the non-noxious range made an improvement on the threshold of stimulus detection could be accounted for by different mechanisms than are involved in pain-touch interactions. Within the non-noxious range of thermal stimulation, Kenton and colleagues observed that SA cutaneous mechanoreceptors were more responsive in the presence of heat (Kenton, Crue, and Carregal 1975; Kenton, Crue, and Carregal 1976). This, in effect, would explain a reduction in threshold, but would not explain a reduction in

influence of conditioning or adapting stimuli, particularly in the time course that was studied (1-5 secs). Rather, the hyper-excitability produced in the presence of warmth could very well be offsetting the balance in excitation and inhibition that is normally present cortically. It should also be noted that a change in balance of excitation and inhibition via hypo-excitability, such as that observed with administration of an NMDA receptor blocker, also leads to a similar reduced adaptation effect (Folger et al. 2008). If it is the case that balance of excitation and inhibition is critical for normal adaptive responses, then one prediction that could come from this study is that subjects with less than optimal excitatory/inhibitory balance could actually perform better at the adaptation task in the presence of heat than without. This interesting possibility is currently under investigation, and it is anticipated that metrics, such as those presented in this report, could provide a means for assessing patient populations that have dysfunctional mechanisms for mediating pain-touch interactions without the delivery of painful stimuli, if the current assumption that some of the CNS mechanisms that mediate tactile-thermal and tactile-pain interactions are shared holds true in future studies.

In summary, elevation of skin temperature can lead to decreased vibrotactile detection thresholds, a primary measure of tactile sensitivity. Metrics of derived or secondary percepts – such as amplitude discriminative capacity, show little or no effect. Tertiary measures – such as those involved in both temporal and spatial summation – are impacted significantly by elevation in temperature. Although the improvements in tactile sensitivity could be a result of enhanced peripheral activity, the changes in measures that reflect a decrease in the sensitization to repetitive stimulation are most likely centrally mediated. These centrally mediated changes reflect a change in the balance of excitation to inhibition via either an

increase in excitation, a decrease in inhibition or a combination of both.

CHAPTER 4

ALTERED CENTRAL SENSITIZATION IN SUBGROUPS OF WOMEN WITH VULVODYNIA

This work in this chapter has been reported in: Zhang Z, Zolnoun D, Francisco EM, Holden JK, Tommerdahl M. (2011) Altered central sensitization in subgroups of women with vulvodynia. Clin J Pain. Accepted.

4.1 Abstract

To investigate the clinical correlates of central nervous system (CNS) alterations among women with vulvodynia, altered central sensitization has been linked to dysfunction in CNS inhibitory pathways (e.g. GABAergic), and metrics of sensory adaptation, a centrally mediated process that is sensitive to this dysfunction, could potentially be used to identify women at risk of treatment failure using conventional approaches. Twelve women with vulvodynia and twenty age-matched controls participated in this study, which was conducted by sensory testing of the right hand's index and middle fingers. The following sensory precepts were assessed: 1) vibrotactile detection threshold; 2) amplitude discrimination capacity (defined as the ability to detect differences in intensity of simultaneously delivered stimuli to two fingers); and 3) a metric of adaptation (determined by the impact that applying conditioning stimuli have on amplitude discriminative capacity). Participants did not differ on key demographic variables, vibrotactile detection threshold, and amplitude discrimination capacity. However, we found significant differences from controls in adaptation metrics in

one subgroup of vulvodynia patients. Compared to healthy controls and women with a shorter history of pain (n=5; duration (yr) = 3.4 ± 1.3), those with a longer history (n=7; duration (yr) = 9.3 ±1.4)) were found to be less likely to have adaptation metrics similar to control values. Chronic pain is thought to lead to altered central sensitization, and adaptation is a centrally mediated process that is sensitive to this condition. This report suggests that similar alterations exist in a subgroup of vulvodynia patients.

4.2 Introduction

Vulvodynia is a heterogeneous family of idiopathic pain disorders affecting upward of 16% of reproductive age women in the US (Danby and Margesson 2010). It is characterized by both provoked and unprovoked pain in and surrounding vulvar skin, mucosa and underlying musculature. Clinically, vulvodynia is classified into subgroups based on anatomical location (vulvar mucosa vs. hairy/non-hairy epithelium) and temporal characteristics as provoked vs. unprovoked. While a given patient may experience both provoked and unprovoked pain, the most common complaint is that of provoked pain on contact, precipitated by tampon use or intercourse. Unlike unprovoked pain -where the clinical examination is non-specific- the majority of women with provoked pain have localized tenderness in vulvar mucosa (a.k.a. vestibule) (Harlow, Wise, and Stewart 2001). Additionally, women with provoked vulvodynia tend to be younger, and in most instances unaware of their condition until coital debut or the first attempt at using a tampon.

While both peripheral and central abnormalities have been implicated in vulvodynia, the extent to which peripheral vs. central factors contribute to the pain state in an individual patient remains unknown. A substantial portion of women with vulvodynia show

hypersensitivity at extra-genital sites (e.g. arms and feet); this non-specific hypersensitivity has conventionally been attributed to changes in 'central sensitization' caused by the chronic pain state. To date, clinical signs and symptoms associated with central dysregulation in subgroups of women with vulvodynia remains unknown. Thus, understanding of the mechanistic (central vs. peripheral) implication of clinical signs and symptoms in vulvodynia is a necessary first step towards individualized, symptom based treatment approach.

Current literature (Danby and Margesson 2010; Giesecke et al. 2004; Gunter 2007) suggests that symptoms of vulvodynia are likely to be triggered by peripheral factors in the skin and/or underlying musculature. With time (and chronicity), varying degrees of central dysregulation may develop. In this setting, patients may experience superimposed unprovoked (spontaneous) pain in otherwise unaffected tissue. Thus, investigating clinical correlates of central involvement in vulvodynia (e.g., how sensory information processing is altered) may provide us with a unique opportunity to investigate the mechanisms of clinically similar disorders (e.g. localized pain at the vulvar vestibule vs. generalized vulvar pain). Once the fundamental mechanisms of the centrally vs. peripherally mediated vulvar pain is understood, this knowledge will enable the development of robust research and clinical tools that could improve diagnosis and lead to informed therapeutic options.

In this study, we investigated sensory information processing in subgroups of patients with vulvodynia and healthy controls. The quantitative sensory testing methodology utilized in this study has been demonstrated to be sensitive to systemic cortical alteration (Folger et al. 2008; Tannan et al. 2008; Tommerdahl, Tannan, Cascio, et al. 2007), and in pilot studies, has been shown to return to normative values with treatment (Tommerdahl; personal communication, 2010). In this study, we hypothesized that women who had experienced a

longer time course with pain and/or had unprovoked symptoms are more likely to have measures consistent with altered central sensitization when compared to healthy control subjects or those subjects who had experienced a shorter duration of provoked pain.

4.3 Methods

In this study, a convenience sample of twelve women with vulvodynia and twenty healthy controls without gynecological pain were recruited from the University of North Carolina, Pelvic Pain Clinic and the surrounding community, respectively. The groups did not differ in basic demographic characteristics. All the participants were naïve both to the study design and issue under investigation. The study was performed in accordance with the Declaration of Helsinki, all subjects gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

Experimental sessions were conducted with the subjects seated comfortably in a chair with the right arm resting on an arm rest attached to the head unit of a portable four-site vibrotactile stimulator (Figure 4.1; CM4; Cortical Metrics, LLC). Vibrotactile stimulation was conducted via 5mm probes that come in contact with subject's digit 2 (index finger) and digit 3 (middle finger). Glabrous pads of digit 2 (D2) and digit 3 (D3) were chosen as the test sites for two reasons: (1) to allow the convenience of access and comfort of the subject, and (2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of cortex in primates. The independent probe tips are computer controlled and capable of delivery of a wide range of vibrotactile stimulation of varying frequencies (measured in Hertz) and amplitudes (measured in micrometers, μm).

Stimulus parameters are specified by test algorithms that are based on specific protocols and subjects' responses during those protocols.

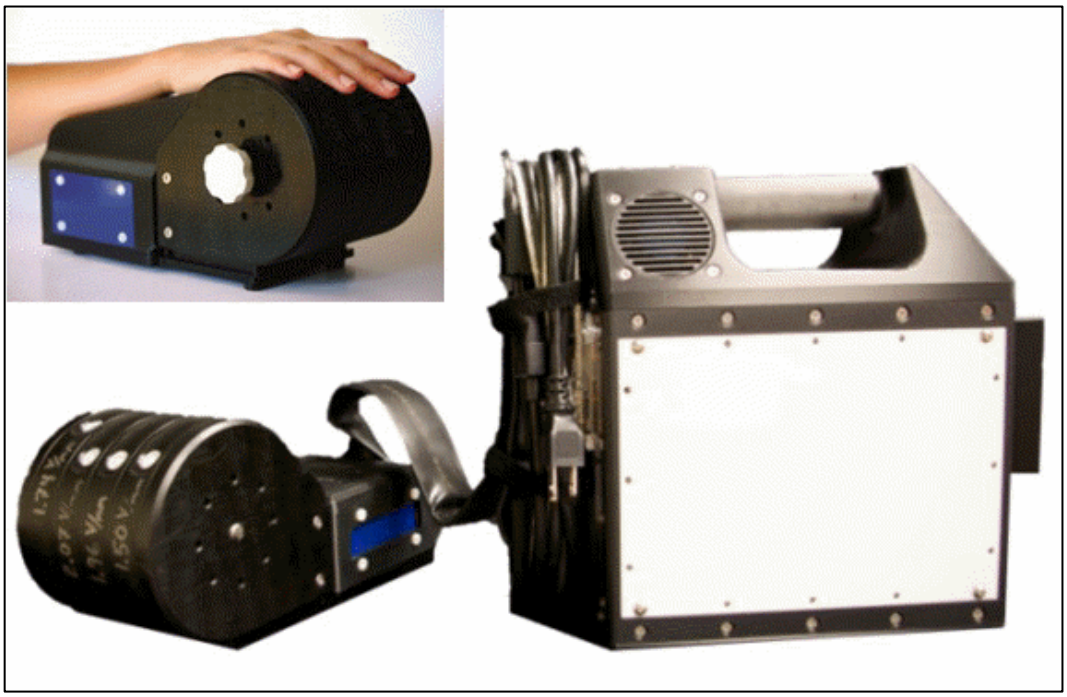

Figure 4.1 Images of the multi-site vibrotactile stimulator. Stimulators are positioned by rotating each of the 4 independently positioned drums to maximize contact between fingers and the stimulator tips. During an experimental session, the subject was seated comfortably in a chair with the right arm resting on the arm rest attached to the head unit of the stimulator. Index and middle finger were positioned for D2 and D3 stimulation.

Participants viewed a computer monitor which provided continuous visual cueing during the experimental session. Specifically, an on-screen light panel indicated to the subject when the stimulus was on and when the subject was to respond. Practice trials were performed before each test which allowed the subject to become familiar with the tests, and correct responses on 5 consecutive training trials were required before commencing with each test. The subject was not given performance feedback or knowledge of the results during data acquisition.

The sensory testing session was conducted by application of low frequency (25 Hz) vibration to right hand's index and middle finger(s). The protocols –from start to finish- lasted approximately 30 minutes and consisted of the following 5 modules: (1) static detection threshold; (2) dynamic detection threshold; (3) amplitude discrimination between two concurrent and stationary stimuli; (4) the impact of single-site adaptation on amplitude discrimination capacity; and (5) dynamic amplitude discrimination. Exemplary use, technical description and neurobiological basis of individual modules have previously been described in detail (Folger et al. 2008; Francisco et al. 2008; Tannan et al. 2008; Tannan, Simons, et al. 2007; Tommerdahl, Tannan, Cascio, et al. 2007; Zhang et al. 2009). An overview of the procedures and the previously published normative findings is provided below.

Static detection threshold - Each participant's vibrotactile detection threshold was measured using a 20-trial Two Alternative Forced Choice (2AFC) tracking protocol (for recent description with this experiment setup, see previous studies (Francisco et al. 2008; Tannan, Dennis, and Tommerdahl 2005; Tannan, Dennis, and Tommerdahl 2005; Tannan, Whitsel, and Tommerdahl 2006; Zhang et al. 2009)). The left panel of Figure 4.2a shows the schematic of the protocol. During each trial a 25 Hz vibrotactile test stimulus was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis in order to minimize subject's inattention and distraction. Following each vibrotactile stimulus, the subject was prompted to select the skin site (index (D2) vs. middle (D3) finger) that was perceptually larger. After a 5 sec delay –based on subject response- the stimulation was repeated until the completion of the 20 trials. The stimulus amplitude was started at 15 μm and was modified based on the subject's response in the preceding trial. A 1-up/1-down algorithm was used for the purposes of amplitude modification in the first 10 trials. For

example, the stimulus amplitude was decreased by 1 μm if the subject's response in the preceding trial was correct. However, it was increased by the same amount if the response was incorrect. After the initial 10 trials, the amplitude was varied using a 2-up/1-down algorithm (two correct/one incorrect subject response(s) resulted in a decrement/increment, respectively, in the amplitude of the stimulus). The rationale for using 1up/1down algorithm in the first 10 trials was to expedite determination of subject's vibrotactile discriminative range without affecting the results, and this approach has been previously reported (Tannan, Dennis, et al. 2007; Tannan et al. 2008; Zhang et al. 2009; Zhang et al. 2008; Folger et al. 2008; Francisco et al. 2008; Tannan, Simons, et al. 2007).

Dynamic detection threshold - At the beginning of each trial (as shown in Figure 4.2a, right panel), a delay period which includes no stimulation was applied. Four conditions of delay (n sec) were employed, in separate trials: 0, 1.5, 2, and 3 sec. After the initial delay, a 25 Hz vibrotactile stimulus was delivered to either D2 or D3 (the stimulus location was randomly selected on a trial-by-trial basis). The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/sec. The subject was instructed to indicate the skin site that received the stimulus as soon as the vibration was detected. The subject's detection threshold was calculated as the average of the stimulus amplitude at the time of subject response (msec).

Amplitude discrimination at baseline - Each subject's amplitude discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies (Tannan, Dennis, et al. 2007; Tannan et al. 2008; Zhang et al. 2009; Zhang et al. 2008; Folger et al. 2008; Francisco et al. 2008; Tannan, Simons, et al. 2007). As shown in Figure 4.2b left panel, during the 20-trial experimental run,

a vibrotactile test stimulus (25 Hz, amplitude between 105 and 200 μm) was delivered to one digit pad at the same time that a standard stimulus (25 Hz, amplitude fixed at 100 μm) was applied to the other digit pad. The loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. At the beginning of the experimental run, the test amplitude was 200 μm and the standard amplitude was 100 μm. The difference between the amplitudes of the test and standard stimuli was adjusted on the basis of the subject's response in the preceding trial, such that the difference was decreased/increased after a correct/incorrect response, respectively. The same tracking algorithm as that described for the tactile detection threshold protocol (2AFC tracking protocol) was employed to track the subject's ability to determine the most intense stimulus between the test and standard stimuli (i.e., the subject's difference limen (DL) was determined). The step size was held constant at 10 μm throughout the experimental run.

Dynamic amplitude discrimination - To further characterize the effects of adaptation on amplitude discrimination, a dynamic tracking protocol was implemented (for recent description with this experimental setup, see previous study (Zhang et al. 2009)). At the start of each run (shown in Figure 4.2c), two vibrotactile stimuli (25 Hz; initially identical in amplitude at 300 μm) were delivered simultaneously to D2 and D3. Four conditions of initial constant stimulus duration (n sec) were employed in separate experimental trials: 0, 1.5, 2, and 3 sec. After the initial constant or stationary stimulus period, the amplitudes of both stimuli were dynamically altered such that the amplitude of one stimulus was increased and the amplitude of the other stimulus was decreased at the rate of 25 μm/sec. The subject was instructed to indicate the location at which the most intense stimulus was delivered as soon as the two stimuli felt distinctly different in intensity. For each trial, the DL was

recorded as the actual difference between the two test amplitudes at the time of subject response (m sec). Averaged DLs were obtained for the four different durations of conditioning stimuli that preceded each trial.

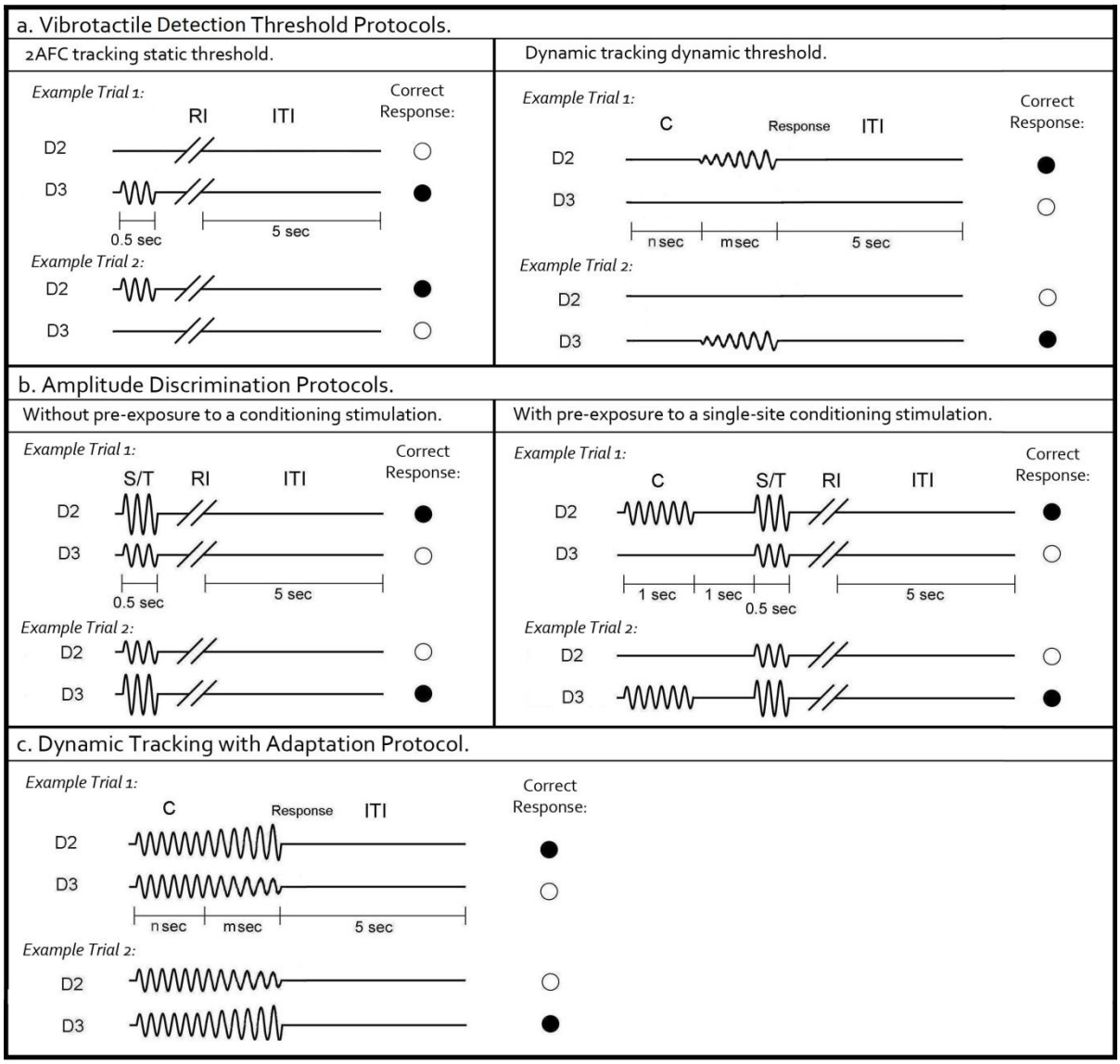

Figure 4.2 Schematics of the experimental protocols used in this study.

Analysis. Repeated-measures analysis of variance (ANOVA) was used to evaluate the difference of the subject's performance under different conditions. Data are presented as

means and standard errors (SE). A probability of less than 0.05 was considered statistically significant.

4.4 Results

The present study compared women with vulvodynia and matched healthy controls in a series of sensory perceptual measures that assessed: (1) vibrotactile detection threshold on the fingertip; (2) amplitude discrimination capacity; and (3) the impact of conditioning stimuli on amplitude discrimination capacity. The results show that patients with vulvodynia deviated very little from that of healthy controls in most of the sensory measures obtained in the absence of conditioning stimuli – such as threshold detection and amplitude discriminative capacity, although the patients with vulvodynia demonstrated a tendency to have lower tactile thresholds on the fingertips than controls. Most importantly, the measures of the effects of conditioning stimuli on amplitude discrimination revealed that the patients' data clustered into two distinct sub-groups (which will be referred to as Group A and Group B). Group B data was very similar to that obtained from healthy control subjects, and Group A demonstrated a significantly reduced impact of adaptation on the sensory percept. While the average ages and demographics of the two sub-groups were not significantly different, there was a significant difference in the duration that the two sub-groups of patients had pain: Group A (n=7) subjects had suffered from vulvodynia for a long duration (average duration: 9.3 ± 1.4 years; average age: 35.7 ± 3.2 years); and Group B (n=5) subjects had suffered from vulvodynia for a relatively shorter duration (average duration: 3.4 ±1.3 years; average age: 34.6 ± 4.3 years).

Patients with vulvodynia exhibit slightly lower tactile detection thresholds. Figure 4.3 summarizes the group-averaged detection thresholds. As shown in the left panel of Figure 4.3, the group-averaged static thresholds observed were 12.37±1.34 μm for controls, 9.77±2.23 μm for patients in Group A, and 10.32±1.85 μm for patients in Group B. The data suggest an elevated sensitivity for patients with vulvodynia compared to controls, although this difference was not statistically significant (Group A vs. controls: $p=0.35$; Group B vs. controls: $p=0.51$). This finding is consistent with data reported by Pukall (Pukall et al. 2002) which showed that women suffering from vulvodynia had a lower tactile threshold than controls at sites distant to the genitalia area.

Since several studies have reported that psychophysical measurement methods had a significant influence on vibrotactile thresholds (Maeda and Griffin 1995; Morioka and Griffin 2002), in current study, the subject's vibrotactile threshold was also measured by a dynamic tracking protocol. The group-averaged dynamic thresholds are shown in the right panel of Figure 4.3. There was no significant difference between the controls and two vulvodynia patients groups, although data from patients in Group B showed a lower (though not statistically significant) dynamic threshold than controls.

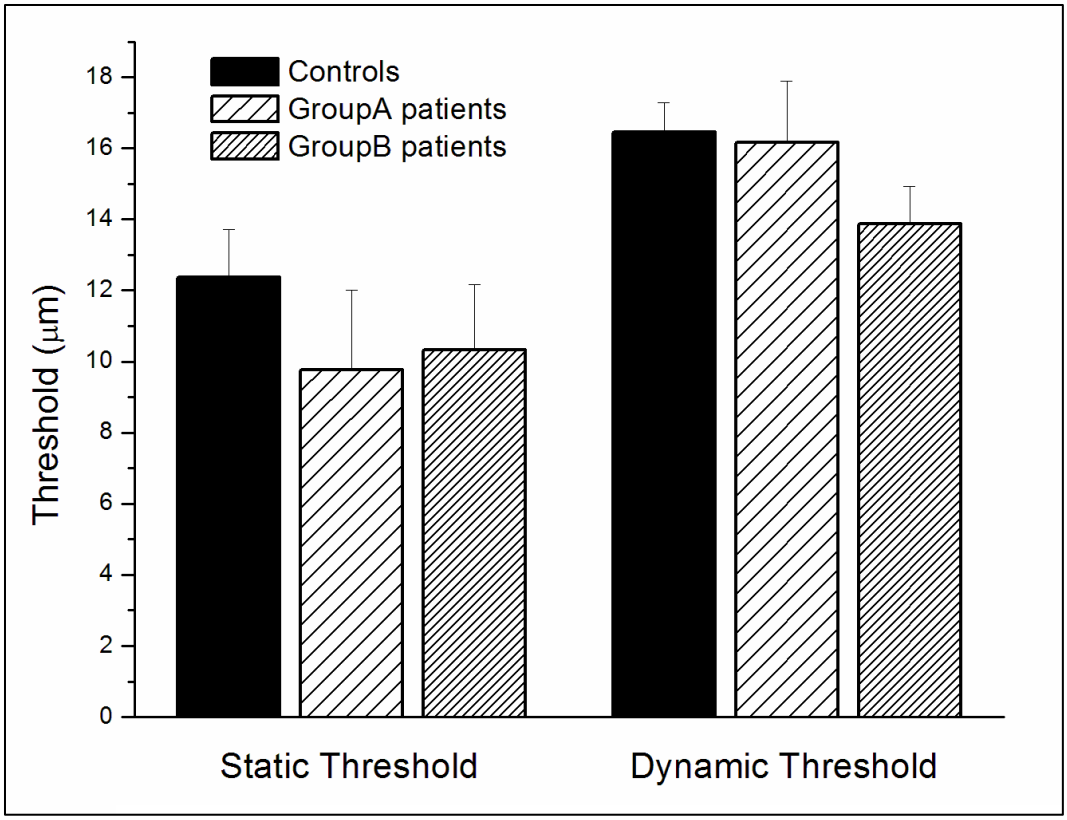

Figure 4.3 Summary of group-averaged vibrotactile detection thresholds obtained with two different methods on two sub-groups of patients with vulvodynia and controls. No significant difference was observed on the static thresholds between any patients group and controls. The group-averaged dynamic thresholds of patients with vulvodynia did not significantly differ from that of controls, while data from patients in Group B show a trend for lower dynamic threshold than controls.

While amplitude discrimination capacity was not significantly different between the controls and patients with vulvodynia, the impact of conditioning stimuli on performance during this task revealed that the vulvodynia subjects were clustered into two distinct sub-groups. Figure 4.4 summarizes the group-averaged performance during amplitude discrimination tests for the controls and two sub-groups of patients with vulvodynia. Weber's fractions (WF) were determined by normalizing each subject's DL to the amplitude of standard stimulus (100 μm). As shown in the left panel of Figure 4.4, during

which amplitude discrimination was measured in the absence of conditioning stimulus, there was no significant difference in performance between the controls and groups of vulvodynia patients. Specifically, control subjects were able to discriminate the difference between the test and standard stimuli that is 24.4% of the standard amplitude (WF = 0.244), and the patients in Group A and Group B were able to discriminate respectively 33.5% (WF = 0.335) and 31.6% (WF = 0.316) of the standard amplitude. However, pre-exposure to a single-site conditioning stimulus dramatically changed the subjects' performance (shown in Figure 4.4, right panel). While the WF of controls and patients in Group B is significantly elevated in the adapted condition compared to the un-adapted condition, patients in Group A performed equally well under both adapted and un-adapted conditions. Previous reports have demonstrated that single-site adaptation impairs control subject's amplitude discrimination capacity (Tannan, Dennis, et al. 2007; Tannan et al. 2008; Zhang et al. 2009; Zhang et al. 2008; Folger et al. 2008; Francisco et al. 2008; Tannan, Simons, et al. 2007). One interpretation of the impairment observed in current study is that a 1 sec conditioning stimulus reduces the perceived intensity of the subsequent test stimulus to the extent that a test stimulus with amplitude of approximately 162% (controls)/ 171% (Group B) of the standard amplitude was perceived nearly the same in intensity as the standard stimulus. Comparing to the significant degradation of performance of the controls ($p < 0.01$) and the patients in Group B ($p = 0.017$) due to adaptation, no change was observed in the patients in Group A ($p = 0.52$). Moreover, under the adapted condition the group-averaged performance is significantly different between controls and patients in Group A ($p = 0.036$). Therefore, conditioning stimulation significantly impaired the performance of the controls and the patients in Group B, but has no effects on the patients in Group A.

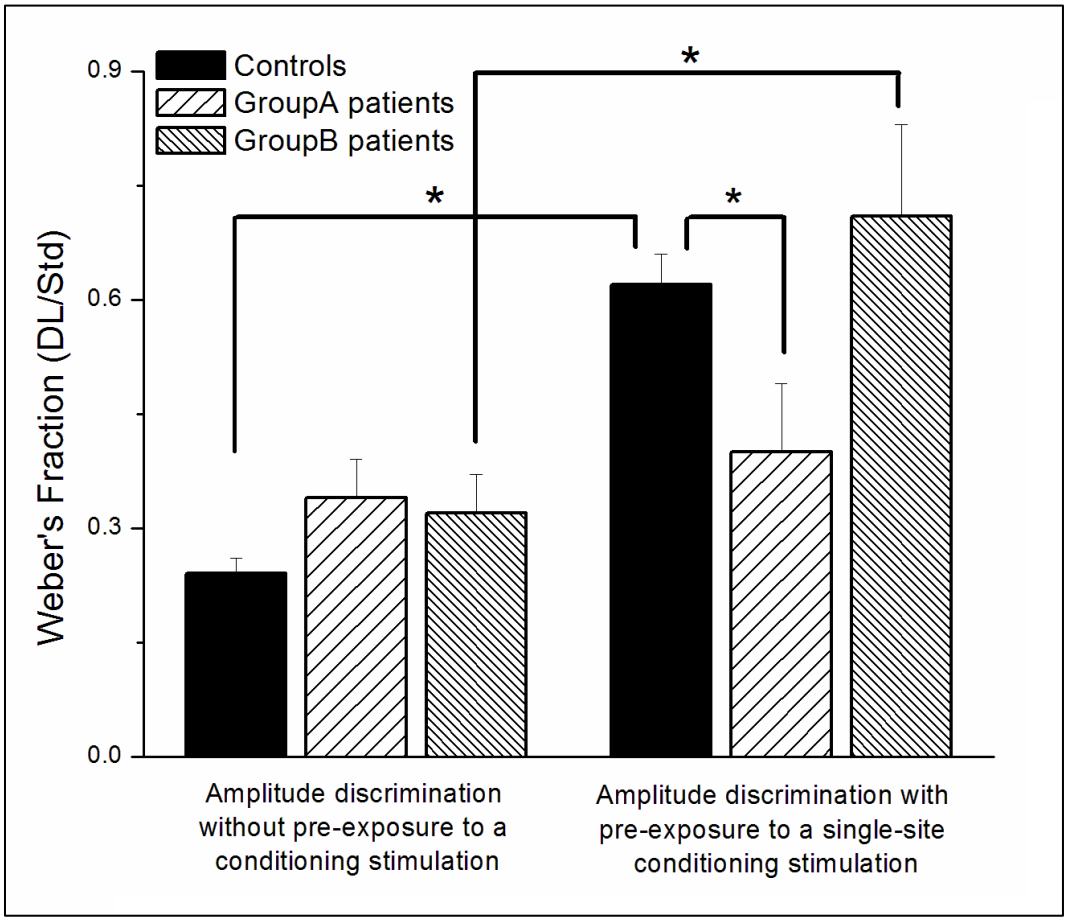

Figure 4.4 Comparison of Weber's fraction obtained with amplitude discrimination protocols (without/with pre-exposure to a single-site conditioning stimulus). In the absence of conditioning stimulus, no significant difference was observed between the performance of controls and sub-groups of vulvodynia patients. Pre-exposure to a single-site conditioning stimulation causes a significant degradation of performance in the controls and the patients in Group B. However, patients in Group A performed equally well under both adapted and un-adapted conditions.

In order to determine whether the differential effects of adaptation observed between groups were consistent within subjects, each subject's WF obtained under the adapted condition was normalized to the un-adapted condition. As shown in Figure 4.5, The 1 sec conditioning stimulus significantly impaired amplitude discrimination capacity by nearly 30%

for both the controls and the patients in Group B, while there was much less of an effect (3%) of adaptation observed in the patients in Group A ($p < 0.01$).

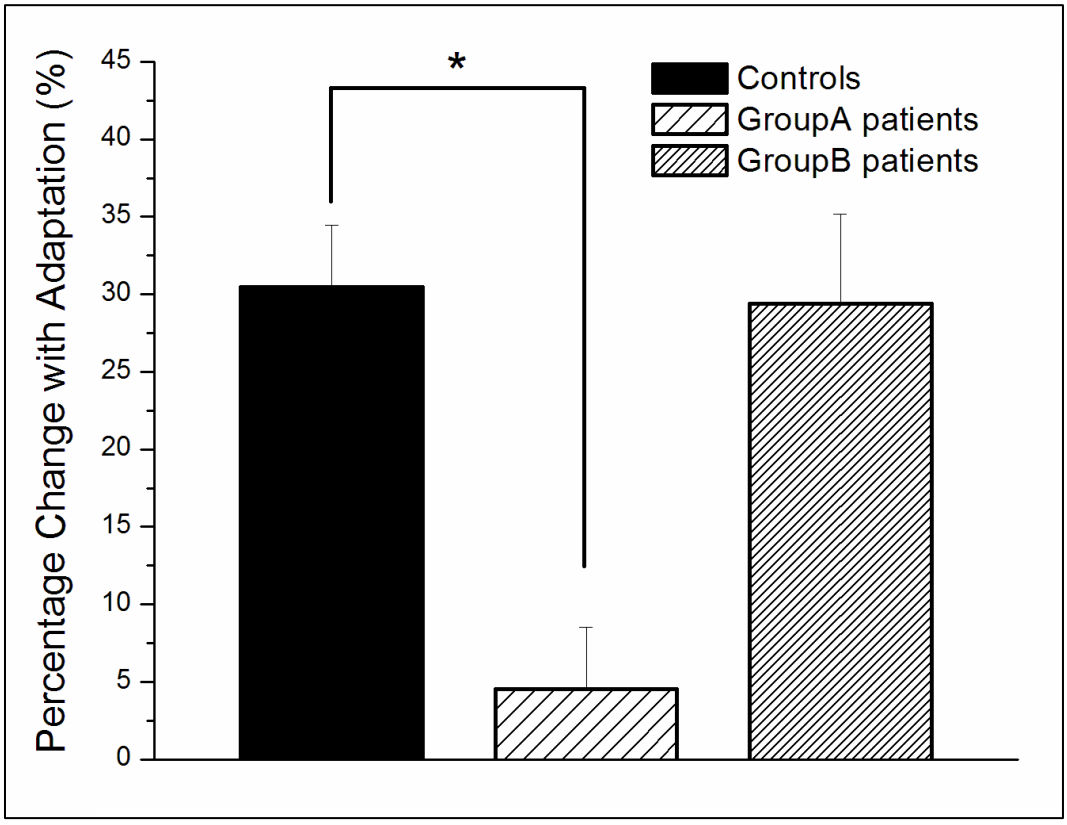

Figure 4.5 Summary of percentage change with adaptation on amplitude discrimination capacity. The WF obtained under the condition with adaptation was normalized to the un-adapted condition on a subject-by-subject basis. Adaptation impaired the subject's amplitude discrimination capacity by nearly 30% for both the controls and the patients in Group B, while much less effect of adaption (3%) was observed in the patients in Group A.

Dynamic amplitude discrimination. A dynamic amplitude discrimination protocol was employed which is able to effectively compare the degree to which a subject adapts to simultaneously delivered dual-site vibrotactile stimuli at different durations of conditioning stimulation. Figure 4.6 summarizes the group-averaged performance with dual-site adaptation at the four different durations of conditioning stimulation (0, 1.5, 2, and 3 sec) for the controls and two sub-groups of patients with vulvodynia. The results show that increasing

the duration of the conditioning stimuli delivered to both sites of skin led to an improvement of a subject's capacity to detect the difference in amplitude between the two stimuli. For example, after pre-exposure to 1.5 sec, 2 sec, or 3 sec conditioning stimulus, control subjects were, on average, able to attain a DL (156 µm, 141 µm, 94 µm) that was ~73%, ~66%, or ~42% of the DL (208 µm) obtained without adaptation. Compared to controls, two sub-groups of patients with vulvodynia have distinct performance differences. Specifically, the DLs were significantly higher in patients of Group A compared to controls (0 sec adaptation: $p < 0.01$; 1.5 sec adaptation: $p = 0.01$; 2 sec adaptation: $p < 0.01$; 3 sec adaptation: $p = 0.06$), but there was no significant difference between patients of Group B and controls in the DLs obtained under all the conditions. In summary, data obtained from patients in Group A showed little effect with conditioning stimulation while the data obtained from patients in Group B deviated very little from that of controls.

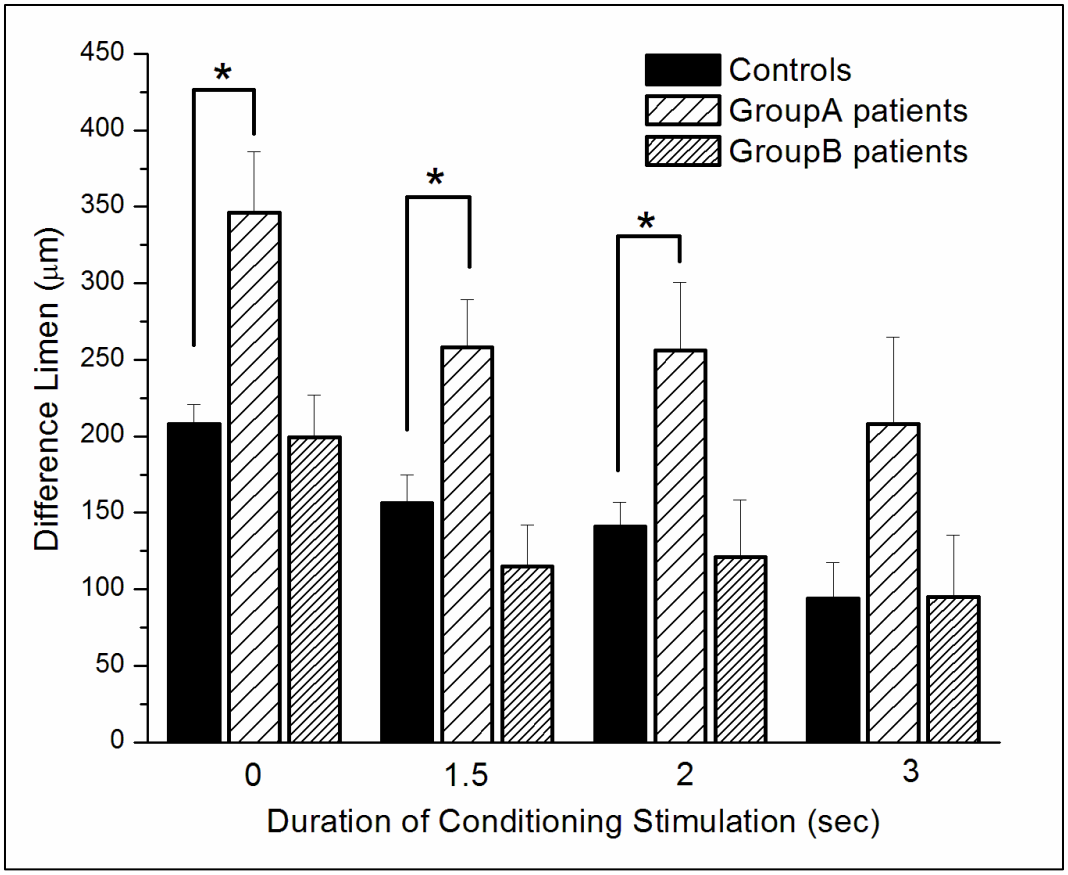

Figure 4.6 Comparison of the group-averaged performance with dual-site adaptation at the four different durations of dual-site conditioning stimulation (0, 1.5, 2 and 3 sec) for the controls and two sub-groups of patients with vulvodynia. Increasing the duration of the conditioning stimuli led to an improvement of performance. As the data obtained from patients in Group B deviated very little from that of controls, DLs obtained from patients in Group A were significantly higher compared to controls and showed only little effect with adaptation.

4.5 Discussion

In this study, sensory perceptual measures were obtained on 12 patients diagnosed with vulvodynia and 20 healthy control subjects. Five tests were performed to assess: (1) detection threshold on the fingertips; (2) amplitude discrimination capacity; (3) the effects of adaptation on tactile discrimination capacity. The results suggest that women with vulvodynia have – although not statistically significantly - lower tactile thresholds on the

fingertips than do control subjects. Furthermore, as amplitude discrimination capacity was not significantly different between the controls and patients with vulvodynia, the impact of single site conditioning (or adaptation) on performance of the dual-site task demonstrated a remarkable difference. Specifically, the observations of the conditioned sensory measures revealed that the patients with vulvodynia were clustered into two distinct sub-groups. Group B had data that was very similar to that obtained from healthy control subjects, while Group A demonstrated a significantly reduced impact of adaptation on the sensory percept. The primary difference between the compositions of the two sub-groups is the duration or longevity of pain of the patients in each sub-group. Group B was composed of patients that reported pain for an average of 3.4 ±1.3 years, while Group A was composed of patients who reported pain for an average duration of 9.3 ± 1.4 years.

The reduction of the adaptation metric in patients with vulvodynia studied in this paper has not been previously reported. There have been few studies to date that have assessed the changes in perception that normally result from repetitive vibrotactile stimulation on the population of chronic pain patients, though Hollins and colleagues did report decreased effects of adaptation in subjects with tempormandibular disorders (Hollins et al. 1996). Neurophysiological studies have demonstrated that repetitive stimulation results in temporal changes of cortical activity, the most prominent of which is a reduction in cortical response with extended stimulus duration. At the single cell level, both visual and somatosensory cortical pyramidal neurons undergo prominent use-dependent modifications of their receptive fields and response properties with repetitive stimulation. These modifications can attain full development within a few tens of milliseconds of stimulus onset, and can disappear within seconds after the stimulus ends (visual cortical neurons (Bredfeldt

and Ringach 2002; Celebrini et al. 1993; Das and Gilbert 1995; DeAngelis et al. 1995; Dinse and Kruger 1990; Pack and Born 2001; Pettet and Gilbert 1992; Ringach, Hawken, and Shapley 1997; Shevelev et al. 1998; Shevelev, Volgushev, and Sharaev 1992; Sugase et al. 1999); alternatively, for review of short-term cortical neuron dynamics in visual cortex (Kohn 2007); for review of short-term primary somatosensory cortical neuron dynamics (Tommerdahl et al. 1998; Tommerdahl, Favorov, and Whitsel 2005; Tommerdahl, Simons, et al. 2005; Tommerdahl, Whitsel, et al. 1996)). Optical imaging studies have also characterized the short-term dynamics of the population-level response of squirrel monkey contralateral primary somatosensory (SI) cortex using different amplitudes and durations of vibrotactile stimulation (Simons et al. 2007; Simons et al. 2005; Chiu et al. 2005). Guided by the scientific work mentioned above, our research group has designed a series of tactile sensory diagnostics which effectively assess the impact that adaptation has on perception (Folger et al. 2008; Francisco et al. 2008; Tannan, Simons, et al. 2007; Tommerdahl, Tannan, Cascio, et al. 2007; Zhang et al. 2009; Zhang et al. 2008). For example, the protocols employed in the current study directly measure the change in amplitude discrimination capacity that occurs with prior conditioning stimuli. Previous studies using this measure demonstrated that a subject's ability to discriminate between two simultaneously delivered vibrotactile stimuli – differing only in amplitude and location – was very robust and repeatable across a large number of healthy subjects, but it was also very sensitive to varying conditions of conditioning stimuli. For instance, changing the duration of the conditioning stimulus delivered to one of the two sites before the amplitude discrimination task significantly altered a subject's ability to determine the actual difference between the two stimuli in a predictive and quantifiable fashion. As a result, these methods could be viewed as a reliable indicator of

the influence of adapting stimuli on central nervous system response, as changes in the peripheral response are not significantly changed at these short stimulus durations (for discussion, see (Francisco et al. 2008; Tannan, Simons, et al. 2007; Tommerdahl, Tannan, Cascio, et al. 2007; Tommerdahl et al. 2008; Tommerdahl, Tannan, Zachek, et al. 2007)). Centrally mediated adaptation is dependent on several factors (e.g., GABAergic and NMDA receptor mediated neurotransmission, neuron-glial interactions) which play significant roles in the way in which cortical information processing capacities of a number of clinically identified subject populations are impacted by their respective disorder. For example, conditioning stimuli do not have as pronounced an impact on the amplitude discriminative capacity of subjects with autism as it does with typically developing subjects (for discussion of GABA-deficiencies in autism, see (Tannan et al. 2008; Tommerdahl, Tannan, Cascio, et al. 2007; Tommerdahl et al. 2008)). Additionally, subjects administered a relatively small dose of an NMDA receptor antagonist (60 mg of dextromethorphan) also demonstrated a degraded adaptation metric (Folger et al. 2008).

Two aspects of the adaptation process were measured in this study. The first, the gain effects of adaptation, was derived from the amplitude discrimination task in which a conditioning stimulus was delivered on one of the two test sites. The effect of that conditioning stimulus was on the gain of the conditioned site – that site was now perceived to be much smaller and thus, a reduction in gain was manifested, and subsequently, subjects (normally) become worse at the task. The second facet of adaptation that was measured was a contrast effect, in which contrast between two stimuli improve after conditioning stimuli have been delivered to both of the test sites, and the subjects (normally) perform better after conditioning than they do without. In this study, the data obtained from the vulvodynia

subjects clustered into two distinct sub-groups consistently with both of these aspects of adaptation. The patients in Group B performed very similar as healthy controls did, and the performance of the patients in Group A showed a significantly reduced impact of conditioning stimulation on the sensory percept. However, other sensory measures obtained in the absence of conditioning stimuli – such as threshold detection and amplitude discriminative capacity – demonstrated no statistically significant difference between the two sub-groups. The primary difference between the compositions of the two sub-groups of note is the duration that patients of the sub-groups have had pain, while average age of the two sub-groups was not significantly different. Considering the metrics of adaptation (measuring the effects of conditioning stimulation on sensory perception) could be a reliable indicator of systemic alterations on central nervous function, it is speculated that the performance difference between the two sub-groups of patients with vulvodynia observed in the current study might reflect the level of dysregulation of their central nervous system due to chronic vulvar pain.

The involvement of both peripheral and central mechanisms in the development and maintenance of vulvodynia has been supported by a series of studies (Giesecke et al. 2004; Pukall et al. 2002; Bergeron et al. 2001; Marinoff and Turner 1991; Bohm-Starke et al. 2001; Pukall et al. 2005; Gordon et al. 2003; Zolnoun et al. 2006). For example, it has been found that patients with vulvodynia have increased sensitivity to sensory stimulation at both genital regions and sites distant to it (Bohm-Starke et al. 2001; Giesecke et al. 2004; Pukall et al. 2002). This suggests that not only peripheral sensitization but also a generalized central abnormality is involved in vulvodynia and could be similar to that observed in patients with other pain syndromes, implying a widespread disturbance in the CNS (Pukall et al. 2005).The

observation of increased tactile sensitivity of the skin area distant to the vulvar region – including the static thresholds of all vulvodynia subjects in this report - is consistent with altered central sensitization that develops with chronic pain.

All subjects, including controls, demonstrated a dynamic threshold that was higher than their static threshold. This noticeable difference in the threshold between the two tasks is consistent with previous reports (Morioka and Griffin 2002; Zhang et al. 2009). Although this could possibly be explained by the influence that psychophysical measurement methods have on tactile detection (Maeda and Griffin 1995; Morioka and Griffin 2002), we believe an alternate explanation is much more plausible. Mechanistically, this phenomenon could be the result of feed-forward inhibition that is generated by the initial subthreshold stimulus that occurs when the threshold test is ramped from zero to the detectable level (Tommerdahl, Favorov, and Whitsel 2010). The significance of this is that this type of feed-forward inhibition takes place in somatosensory cortical input layer 4 (Favorov and Kursun 2011), in which local layer 4 inhibitory cells receive direct thalamocortical input and in turn suppress responses of neighboring layer 4 excitatory cells to their thalamocortical drive, thereby sharpening their RF properties (Douglas et al. 1995; Miller, Pinto, and Simons 2001; Bruno and Simons 2002; Alonso and Swadlow 2005; Sun, Huguenard, and Prince 2006; Cruikshank, Lewis, and Connors 2007). These inhibitory cells are more responsive to weak (near-threshold) afferent drive than are the excitatory layer 4 cells, and thus, sub-threshold or weak stimulus inputs will have the effect of raising the threshold at which excitatory layer 4 cells begin to respond to peripheral stimuli. Thus, though not statistically significant, the observation of the difference between the Group A and B patients in their dynamic thresholds is that the difference between the ratio of the respective dynamic and static thresholds are

clearly evident, and suggestive of below normal feed-forward inhibition. If this alteration is, as we believe, sensitive to the time dependency of the GABAb receptor, then the measure itself might be an indicator that GABAb efficiency has been compromised in some individuals.

Our data on vulvodynia patients is consistent with existing constructs in the pain literature and supports the notion that the relative contribution of peripheral and central factors differ in subgroups of women with vulvodynia, and that clinical signs and symptoms alone are insufficient in identifying the underlying mechanism of pain as peripheral, central or a combination of both. A wide range of therapies for vulvodynia have been proposed that include topical therapies, pharmacologic regimens, physical therapy, surgery, and cognitive behavioral therapy (Goldstein, Marinoff, and Haefner 2005). However, outcomes with these therapies vary widely. For example, as a commonly reported therapy for localized vestivular dysesthesia, vestibulectomy is most effective for a specific subset of patients, specifically women under 30 years old who have localized vulvar pain and provoked pain (Traas et al. 2006; Bornstein et al. 1997). These findings suggest that it's possible that this type of pain represents a localized nociceptor mechanism, while unprovoked and generalized pain could have a different mechanism. Our data suggest that women suffering vulvar pain for long duration or with unprovoked pain have more CNS involvement or dysregulation. The CNS involvement occur de novo (e.g. genetic polymorphism) or secondary to an intractable pain state; the latter is the likely mechanism by which women with provoked vulvodynia transition into unprovoked and/or chronic pain state. It is well documented that an intractable peripheral process can lead to neuroplastic changes (via central sensitization) at all levels of the CNS and "generalization of pain" (Woolf and Doubell 1994).

The findings in this study are consistent with the idea that chronic pain, caused by vulvodynia, alters central sensitization that leads to changes in sensory information processing. These changes are manifested in lower sensory thresholds (or higher sensitivity) in sites without provoked pain – because of a change in the balance between excitation and inhibition (or glutamatergic and gabaergic neurotransmission). Lower thresholds are consistent with this imbalance; decreasing inhibition will result in less suppression of cortical activity. In other words, a simple stimulus on the skin will generate more cortical activity if altered central sensitization has resulted in decreased inhibition or increased excitation. However, threshold testing has not been considered as an efficient method in measuring altered central sensitization due to large inter-individual variability. And in order to show these small differences, group differences of repeated measurements are normally necessary. Alternatively, using a measure – such as an adaptation metric – in which the patient provides their own individual baseline (i.e., the adaptation metric is derived on how amplitude discriminative capacity is impacted by conditioning) – could prove to be a more effective indicator of altered central sensitization that can be obtained reliably and efficiently (protocols employed in the current study can be obtained within 2-3 minutes). Sensory based measures of altered central sensitization appear to differentiate chronicity within subgroups of vulvodynia, and future studies will continue to investigate the changes in sensitization that appear to occur with the time course of the history of vulvodynia.

CHAPTER 5

CORTICAL-CORTICAL INTERACTIONS IN THE AGING POPULATION

This work in this chapter has been prepared in: Zhang Z, Francisco EM, Holden JK, Dennis RG, Tommerdahl M. (2011) Cortical-cortical interactions in the aging population. Manuscript.

5.1 Abstract

While it is well known that skin physiology – and consequently sensitivity to peripheral stimuli - degrades with age, what is less appreciated is that centrally mediated mechanisms allow for maintenance of the same degree of functionality in processing these peripheral inputs and interacting with the external environment. In order to demonstrate this concept, we obtained observations of processing speed, sensitivity (thresholds), discriminative capacity and adaptation metrics on subjects ranging in age from 18 to 70. The results indicate that although reaction speed and sensory thresholds change with age, discriminative capacity and adaptation metrics do not. The significance of these findings is that similar metrics of adaptation have been demonstrated to change significantly when the central nervous system (CNS) is compromised. Such compromise has been demonstrated in subject populations with autism (Tannan et al. 2008; Tommerdahl, Tannan, Cascio, et al. 2007), chronic pain (Hollins and Sigurdsson 1998; Hollins et al. 1996; Zhang et al. 2011), acute NMDA receptor block (Folger et al. 2008) and with tactile-thermal interactions (Zhang

et al. 2009). Thus, these quantitative measures – since they can be obtained efficiently and objectively, and appear to deviate from normative values significantly with systemic cortical alterations – could be useful indicators of cerebral cortical health.

5.2 Introduction

There have been a number of significant findings related to both the anatomical and physiological degradation that occurs with normal aging. For example, structural and functional neuroimaging studies have consistently shown evidence of age-related reduction of cerebral cortex volume (Driscoll et al. 2009; Fjell et al. 2009; Raz et al. 2005; Resnick et al. 2003) and changes of white matter integrity in healthy older adults (Bartzokis et al. 2003; Gunning-Dixon et al. 2009; Gunning-Dixon and Raz 2000). However, a number of researchers have noted that cognitive performance is relatively stable with normal aging (Morse 1993; Van Petten et al. 2004; Wilson et al. 2002), although some metrics of sensory performance (e.g., thresholds) degrade (Gescheider et al. 1994; Lin et al. 2005; Verrillo 1982; Verrillo, Bolanowski, and Gescheider 2002). In a recent review, Greenwood put forth a hypothesis that with aging, although there is significant evidence of both anatomical and physiological decline, there is no, or even negative, correlation with cognitive performance. Greenwood largely attributes the undefined compensatory mechanism that allows for maintenance of cortical information processing capacity to cortical plasticity (Greenwood 2007; Greenwood and Parasuraman 2010).

Recently, we have developed unique sensory based measures that quantify particular aspects of a subject's central information processing capacity (Folger et al. 2008; Francisco et al. 2008; Tannan, Dennis, and Tommerdahl 2005; Tannan, Dennis, and Tommerdahl 2005;

Tannan, Dennis, et al. 2007; Tannan et al. 2008; Tannan, Simons, et al. 2007; Tannan, Whitsel, and Tommerdahl 2006; Tommerdahl, Tannan, Cascio, et al. 2007; Tommerdahl et al. 2008; Tommerdahl, Tannan, Zachek, et al. 2007; Zhang et al. 2009; Zhang et al. 2008; Zhang et al. 2011). One particular focus of these studies has been on obtaining measures of centrally mediated adaptation – a process that is a fundamental component of cortical plasticity and operates on multiple time scales (for review, see (Kohn 2007)). If cortical plasticity is the mechanism by which cortical information processing capacity is maintained, and if adaptation does, in fact, parallel cortical plasticity, then we would predict that metrics of adaptation would remain constant with normal aging.

In this study, we collected a number of metrics from a wide age spectrum (18 to 70 years). The metrics that we collected can be broadly defined in one of two categories: those that are peripherally biased and those that are predominantly centrally mediated. We predicted that the measures that are peripherally biased would be most sensitive to aging while measures that are predominantly centrally mediated would be less impacted. The results demonstrate that peripherally mediated measures, such as threshold detection, were - as previously reported by others – significantly impacted with increasing age. This is not surprising, as most of these measures are primarily related to skin physiology, and it is well established that sensory thresholds do increase. Centrally mediated measures, such as those that rely mechanistically on cortical information processing properties such as lateral inhibition and/or adaptation, however, did not change with age. We viewed this as being consistent with Greenwood's hypothesis that cortical plasticity was maintained in normal aging and compensates for both anatomical and physiological losses that have been shown to naturally occur with age.

5.3 Methods

In this study, 120 healthy subjects of different ages (18-70 years) were recruited from the students and employees of the University of North Carolina at Chapel Hill. The subjects were divided into six age groups, 20 subjects in each group. A survey about medication and medical history was filled out by each subject before experimental tests to exclude subjects with a history of neurological impairment. All the subjects were naïve both to the study design and issue under investigation. The study was performed in accordance with Declaration of Helsinki, all subjects gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

During an experimental session, the subject was seated comfortably in a chair with right arm resting on an arm rest attached to the head unit of a portable four-site vibrotactile stimulator (Figure 5.1; CM4, Cortical Metrics, LLC). Vibrotactile stimulation was conducted via 5 mm probes that come in contact with subject's digit 2 (index finger) and digit 3 (middle finger) of the right hand. The independent probe tips are computer controlled and capable of delivery of a wide range of vibrotactile stimulation of varying frequencies (measured in Hertz) and amplitudes (measured in micrometers, μm). Glabrous pads of digit 2 (D2) and digit 3 (D3) were chosen as the test sites for two reasons: (1) to allow the convenience of access and comfort of the subject, and (2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of cortex in primates. The subject's left hand was holding a two-button response device. During each test, the subject

was instructed to press the left/right button when the correct stimulus was perceived on the index/middle finger, respectively.

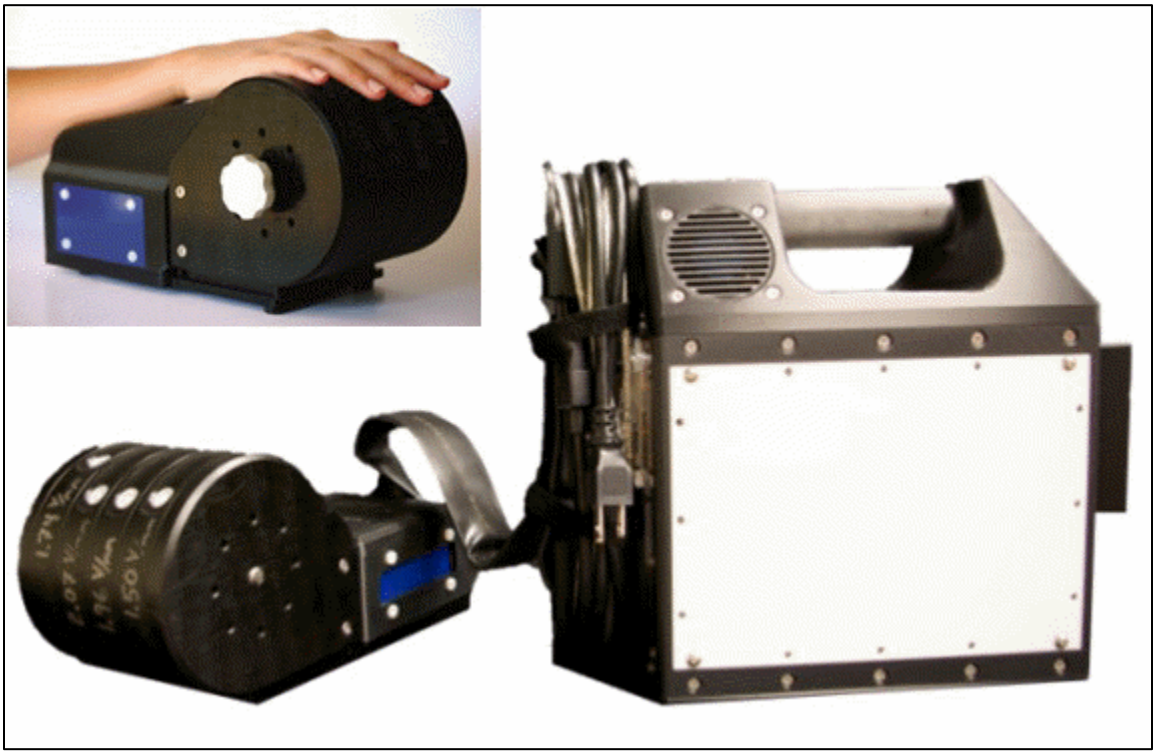

Figure 5.1 Images of the multi-site vibrotactile stimulator. Stimulators are positioned by rotating each of the 4 independently positioned drums to maximize contact between fingers and the stimulator tips. During an experimental session, the subject was seated comfortably in a chair with the right arm resting on the arm rest attached to the head unit of the stimulator. Index and middle finger were positioned for D2 and D3 stimulation.

Visual cueing was provided with a computer monitor during the experimental runs. Specifically, an on-screen light panel indicated to the subject when the stimulus was on and when the subject was to respond. An audiometer was used to make sure that no auditory cues were emitted from the stimulator during delivery of the stimuli. Practice trials were performed before each test which allowed the subjects to become familiar with the test, and correct response on 5 consecutive training trials were required before commencing with each test. The subject was not given performance feedback or knowledge of the results during data

acquisition. Stimulus parameters are specified by test algorithms based on specific protocols and subjects' responses during those protocols.

In the current study, a series of metrics were employed to assess each subject's tactile information processing capacity. The total experiment – from start to finish – lasted approximately 30 minutes and consisted of the following 6 metrics: (1) simple reaction time (RT); (2) choice RT; (3) static detection threshold; (4) dynamic detection threshold; (5) amplitude discrimination between two concurrent stimuli; (6) amplitude discrimination after pre-exposure to a conditioning stimulus to one of the stimulus sites (single site adaptation). Exemplary use, technical description, and neurobiological basis of individual metrics have previously been described in detail (Folger et al. 2008; Francisco et al. 2008; Tannan, Dennis, et al. 2007; Tannan et al. 2008; Tannan, Simons, et al. 2007; Tommerdahl, Tannan, Cascio, et al. 2007; Zhang et al. 2009). An overview of the procedures is provided below.

Simple RT was measured for 14 times during an experimental run for each subject. The left panel of Figure 5.2a shows the schematic of the protocol. During each trial a single tap (amplitude in 300 μm) was delivered to D2. The subject was instructed to press a response button as soon as the tap was felt. After subject's response, a delay between 2 sec and 7 sec was placed before the onset of the next trial. For each trial, the RT was recorded as the time interval between stimulation tap and subject's response. In total, fourteen simple RTs were obtained for each subject. During the course of data analysis, the 2 largest and 2 minimum RT values were excluded in order to eliminate the effects of anticipation and inattention. As a result, a subject's simple RT was calculated as the average of 10 RTs recorded.

Choice RT was measured using a 14-trial Two Alternative Forced Choice (2AFC) protocol. The right panel of Figure 5.2a shows the schematic of the protocol. During each trial a single tap (amplitude in 300 μm) was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis in order to minimize subject's inattention and distraction. The subject was instructed to select the skin site (D2 or D3) that received the tap as fast as possible by pressing the left or right button on the response box. The response accuracy was recorded for each trial. After excluding the 2 largest and 2 minimum values, the average response time of trials with correct response was considered as a subject's choice RT. The average performance accuracy of all the subjects is 95%.

Static detection threshold: Each subject's vibrotactile detection threshold was measured using a 20-trial 2AFC tracking protocol (for recent description with this experiment setup, see previous studies Zhang et al. 2009). The left panel of Figure 5.2b displays the schematic of the protocol. During each trial a 25 Hz vibrotactile test stimulus (lasts 500ms) was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis. Following each vibrotactile stimulus, the subject was prompted to select the skin site (D2 vs. D3) that perceived the stimulation. After a 5 sec delay – based on subject response - the stimulation was repeated until the completion of the 20 trials. The stimulus amplitude was started at 15 μm and was modified based on the subject's response in the preceding trial. During the initial 10 trials, a 1-up/1-down algorithm was used for the purposes of amplitude modification. For example, the stimulus amplitude was decreased by 1 μm if the subject's response in the preceding trial was correct. However, it was increased by 1 μm if the response was incorrect. After the initial 10 trials, the amplitude was varied using a 2-up/1-down algorithm (two correct/one incorrect subject response(s) resulted in a

decrement/increment, respectively, in the amplitude of the stimulus). The rationale for using 1up/1down algorithm in the first 10 trials was to expedite determination of subject's vibrotactile discriminative range without affecting the results, and this approach has been previously reported (Folger et al. 2008; Francisco et al. 2008; Tannan, Dennis, et al. 2007; Tannan et al. 2008; Tannan, Simons, et al. 2007; Tannan, Whitsel, and Tommerdahl 2006; Tommerdahl, Tannan, Cascio, et al. 2007; Tommerdahl et al. 2008; Tommerdahl, Tannan, Zachek, et al. 2007; Zhang et al. 2009; Zhang et al. 2008; Zhang et al. 2011).

Dynamic detection threshold: At the beginning of each trial (as shown in Figure 5.2b, right panel), a delay period (D) which includes no stimulation was applied. Four conditions of delay (n sec) were employed, in separate trials: 0, 1.5, 2, and 3 sec. After the initial delay, a 25 Hz vibrotactile stimulus was delivered to either D2 or D3 (the stimulus location was randomly selected on a trial-by-trial basis). The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/sec. The subject was instructed to indicate the skin site that received the stimulus as soon as the vibration was detected. The stimulus amplitude at the time of subject's response was recorded, and only the value with accurate response was used to calculate the subject's average dynamic detection threshold.

Amplitude discrimination at baseline: Each subject's amplitude discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies (Zhang et al. 2011; Zhang et al. 2008; Zhang et al. 2009; Tommerdahl, Tannan, Cascio, et al. 2007; Tannan, Simons, et al. 2007; Tannan et al. 2008; Tannan, Dennis, et al. 2007; Francisco et al. 2008; Folger et al. 2008). As shown in Figure 5.2c left panel, during the 20-trial experimental run, a vibrotactile test stimulus (T) (25 Hz, amplitude between 105 and 200 μm) was delivered to one digit pad at the same time

that a standard stimulus (S) (25 Hz, amplitude fixed at 100 μm) was applied to the other digit pad. The loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. At the beginning of the experimental run, the test amplitude was 200 μm and the standard amplitude was 100 μm. The difference between the amplitudes of the test and standard stimuli was adjusted on the basis of the subject's response in the preceding trial, such that the difference was decreased/increased after a correct/incorrect response, respectively. The step size was held constant at 10 μm throughout the experimental run. The same tracking algorithm as that described for the tactile detection threshold protocol was employed to track the subject's ability to determine the most intense stimulus between the test and standard stimuli (i.e., the subject's difference limen (DL) was determined).

Adaptation metric: Amplitude discrimination with single-site adaptation. In order to measure the effects that conditioning stimuli have on subsequent test stimuli, the previously described amplitude discrimination protocol was modified such that delivery of the test and standard stimuli was preceded by a single conditioning stimulus to one of the two stimulus sites (as shown in Figure 5.2c, right panel). Specifically, a 25 Hz 200 μm conditioning stimulus (C) was delivered 1 sec prior to the presentation of the test and standard stimuli (S/T). The duration of the conditioning stimulus was 1 sec, which was followed by a 1 sec delay before onset of the simultaneous delivery of the test and standard stimuli. The result of such a protocol modification is that the amplitude discrimination difference limen (DL) is typically significantly elevated after pre-exposure to a single-site conditioning stimulation (Zhang et al. 2011; Zhang et al. 2009; Tannan, Simons, et al. 2007; Tannan et al. 2008; Folger et al. 2008). When the conditioning stimulus is delivered to the same site as the test stimulus, the gain effect of adaptation (reducing the perceived intensity)

can be quantified by comparison of the DL obtained in the adapted vs. non-adapted conditions (amplitude discrimination at baseline). The tracking algorithm used in the previously described protocol was employed.

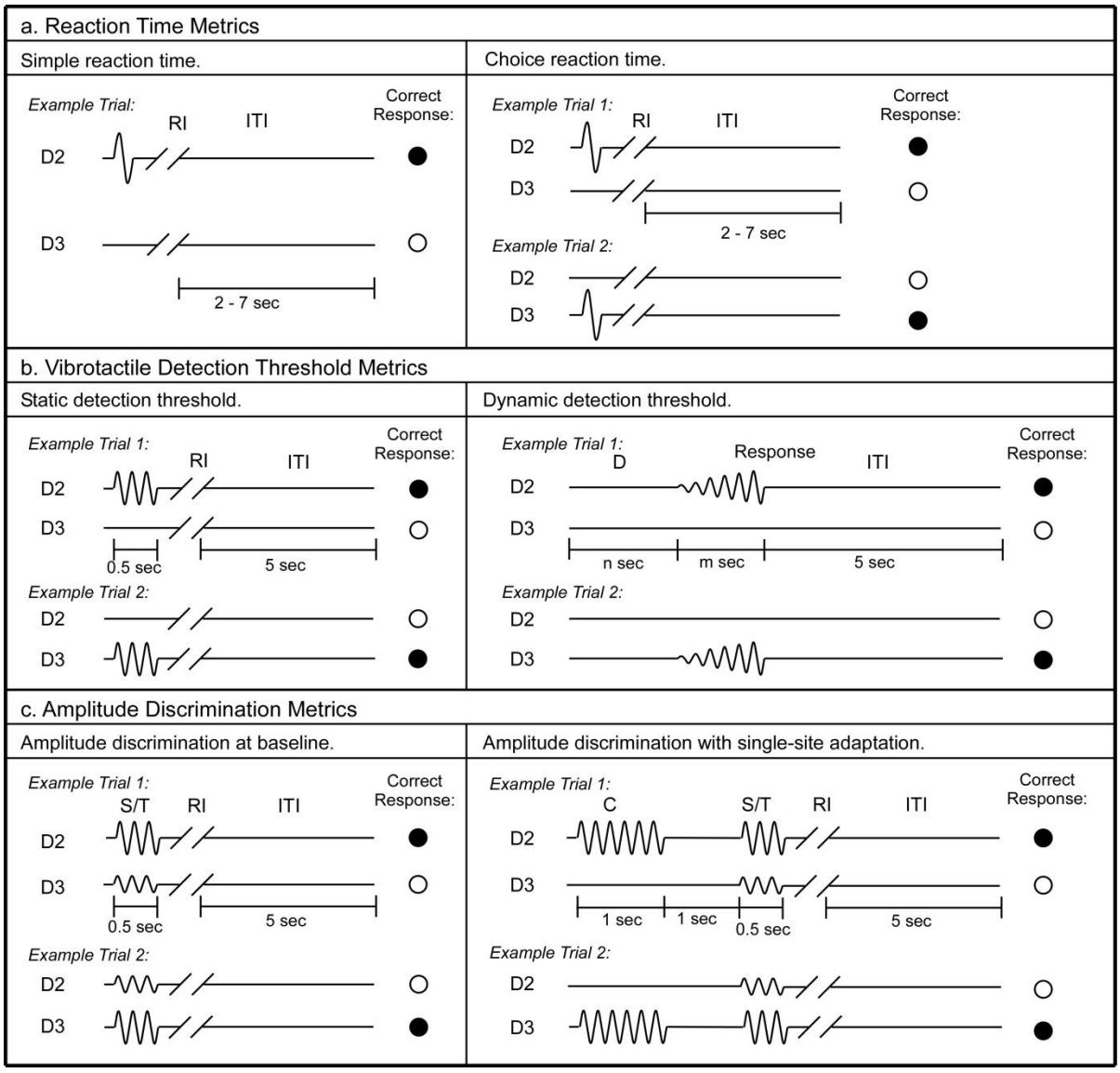

Figure 5.2 Schematics of the experimental protocols used in this study.

Analysis. One way analysis of variance (ANOVA) and two-sample t-test were used to evaluate the difference of the subject's performance across different groups. Data are

presented as means and standard errors (SE). A probability of less than 0.05 was considered statistically significant.

5.4 Results

In the current study, a series of sensory perceptual measures was performed on healthy control subjects of different ages (ranging from 18 to 70 years) that assessed: (1) reaction time; (2) vibrotactile detection threshold; (3) amplitude discrimination capacity; and (4) the impact of adaptation on amplitude discrimination capacity. The results indicate that although RT and sensory thresholds increased as a function of age, the subject's discriminative capacity and the effects of adaptation on performance remained constant across all the age groups tested.

Reaction time increases with aging. Figure 5.3 summarizes the group-averaged RT of six age groups. Both choice and simple RTs progressively increase with advancing age. One way ANOVA was performed to compare the mean RT across six age groups, and there is evidence that there are significant differences in the means across groups ($p < 0.001$ for both simple and choice RT). Two-sample t-test was employed to compare the mean RT of the subjects under 25 years vs. the mean RT of the subject older than 60 years. There is significant difference in the mean simple RT (182 ms vs. 302 ms) and mean choice RT (362 ms vs. 498 ms) with $p < 0.001$. The data suggests an age-related decrement in response speed. Note that for all the age groups, choice RT is always higher than simple RT. The difference between choice RT and simple RT might reflect the duration that it takes for a subject to identify a stimulus location. In Figure 5.4, the group-averaged RT values are plotted against

age. Strong linear relationship (positive correlation) between RTs and age were observed, with R^2=0.99 for simple RT and R^2=0.95 for choice RT.

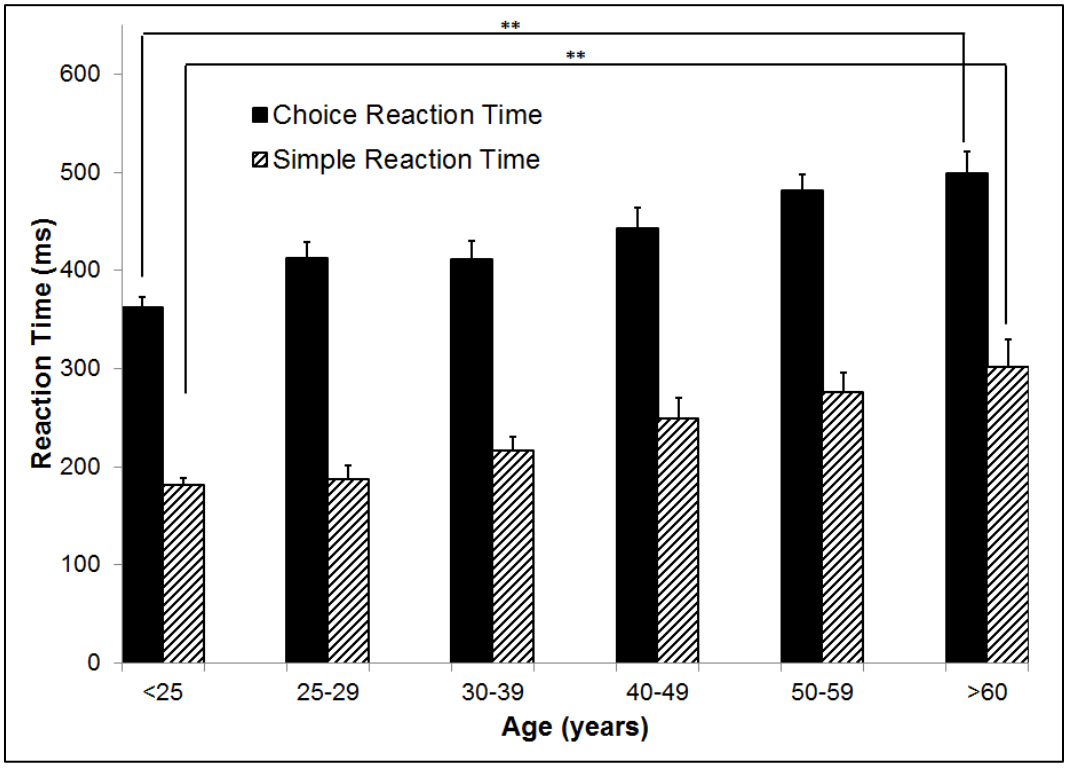

Figure 5.3 Summary of the group-averaged RTs for six age groups. Significant differences in mean simple and choice RT were observed between the subject under 25 years and the subjects older than 60 years.

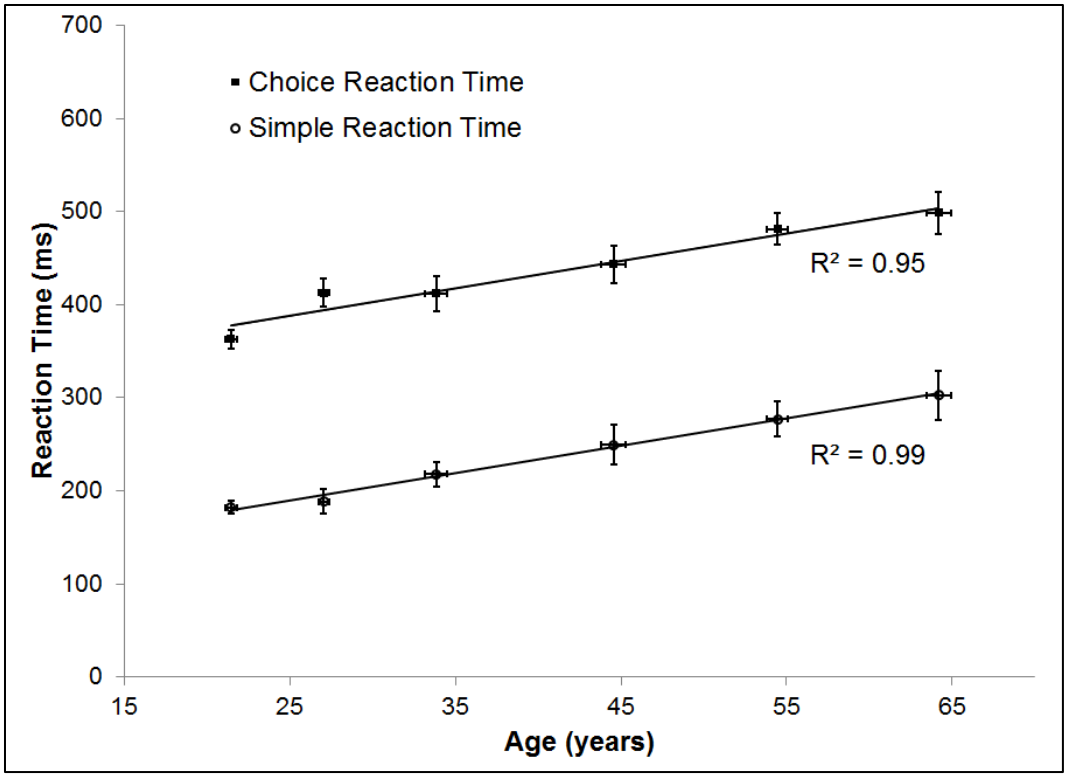

Figure 5.4 Summary of group-averaged RTs plotted against mean age. Strong liner relationship (positive correlation) between RTs and age were observed, with R^2=0.99 for simple RT and R^2=0.95 for choice RT.

In the current study, subject performed each RT test for 14 times. In order to calculate the index of intra-individual variability, the standard deviation (SD) of repeated RT measures was normalized to the mean RT for each subject individually. The group-averaged index of intra-individual variability (%) on RT performance was calculated and plotted in Figure 5.5. One way ANOVA was performed. It was found that there are evidence of significant differences in the means of intra-individual variability for simple RT performance ($p < 0.001$) across six age groups, while no significant differences are found for choice RT performance ($p = 0.11$) across groups. Looking at the intra-individual variability for simple RT by itself, there is no significant differences in the means across age groups younger than 50 years ($p = 0.4$). However, two-sample t-test shows significant difference between mean of 40-49 years

age group and mean of 50-59 years age group ($p < 0.05$). The data demonstrates that the group-averaged intra-individual variability remains relatively constant for the subjects younger than 50 years old, while the older subjects (>50 years) have significant higher intra-individual variability.

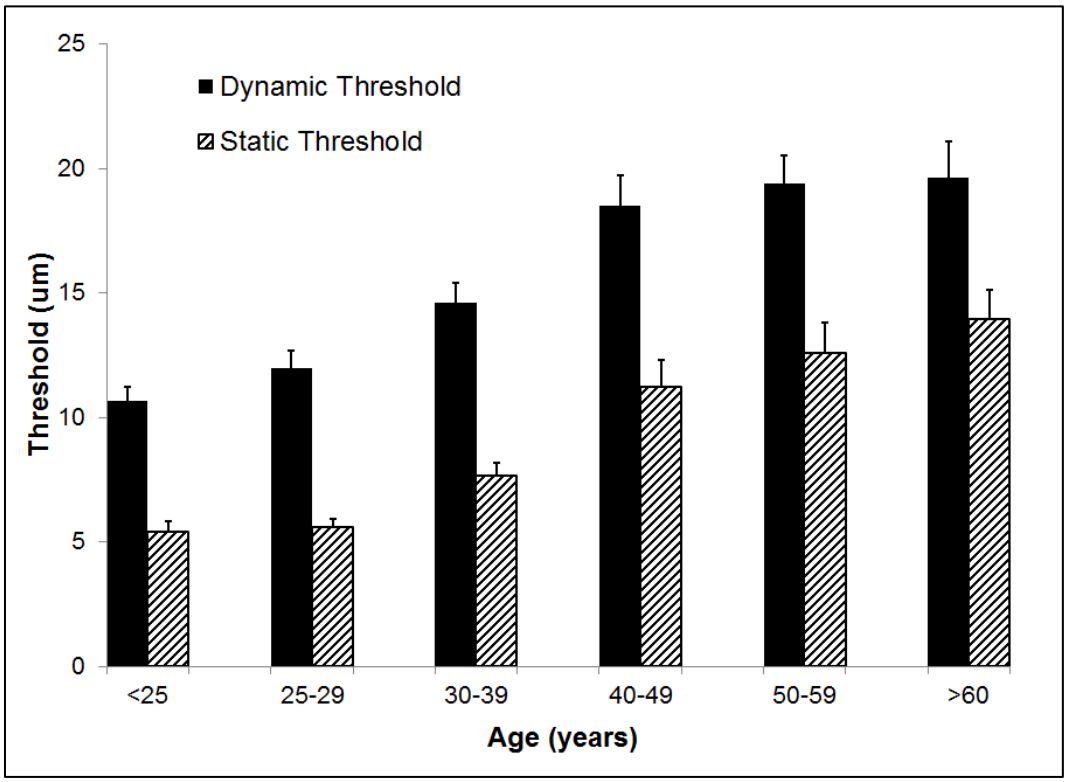

Figure 5.5 Summary of the group-averaged index of intra-individual variability across six age groups. Looking at means of intra-individual variability for simple RT, there is no significant difference in the mean across groups that are younger than 50 years ($p = 0.4$). However, significant difference was found between mean of 40-49 years group and means of 50+ groups ($p < 0.05$). No significant difference was found for choice RT performance across groups ($p = 0.11$).

Vibrotactile detection threshold increases with aging. The group-averaged detection thresholds were obtained with two different methods: a static testing paradigm and a dynamic testing paradigm. As shown in Figure 5.6, the group averaged static threshold gradually increases with advancing age. Specifically, the averaged static threshold for the

subjects who are older than 60 years is 13.95 µm which is about 8 µm larger than that of the subjects under 25 years old (5.42 µm). Since several studies have reported that psychophysical measurement methods had a significant influence on vibrotactile threshold (Maeda and Griffin 1994; Morioka and Griffin 2002), the threshold was also measured by a dynamic tracking protocol, in which a continuously increasing stimulus was delivered. Following the same trend as observed with static testing paradigm, the group averaged dynamic threshold progressively rises with aging. In general, the data suggest an elevated tactile sensitivity for older subjects.

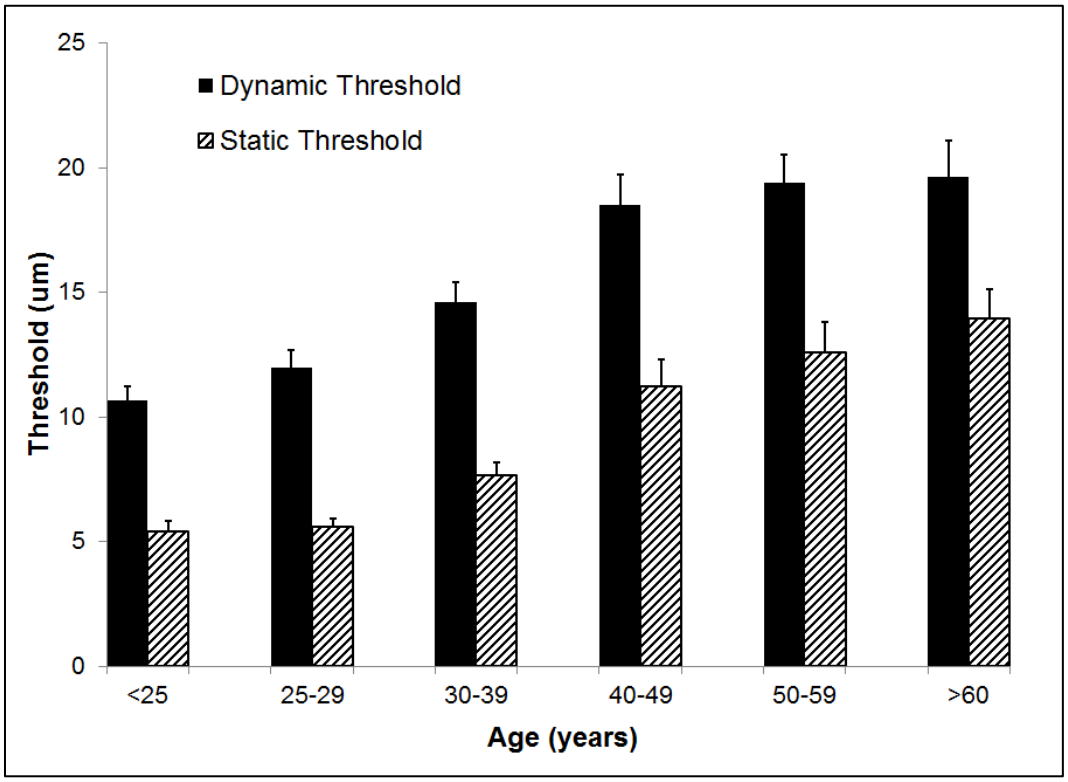

Figure 5.6 Summary of group-averaged vibrotactile detection thresholds obtained with two different methods across six age groups. Both static and dynamic detection threshold progressively rises with aging. All subjects demonstrated a dynamic threshold that was higher than their static threshold.

It is noteworthy that all subjects demonstrated a dynamic threshold that was higher than their static threshold. This noticeable difference in the threshold between the two tasks is consistent with previous reports (Morioka and Griffin 2002; Zhang et al. 2009; Zhang et al. 2011). One of the explanations could be linked to the fact that dynamic threshold is reaction time dependent, while static threshold is independent of reaction time. If this is simply the case, the difference between dynamic and static threshold should be equal to the product of choice RT and the speed of amplitude increment (2 μm/sec) during dynamic threshold measurement. Based on this assumption, we calculated the predicted dynamic thresholds using following equation:

Predicted dynamic threshold = Observed static threshold + Choice RT * 2μm/sec

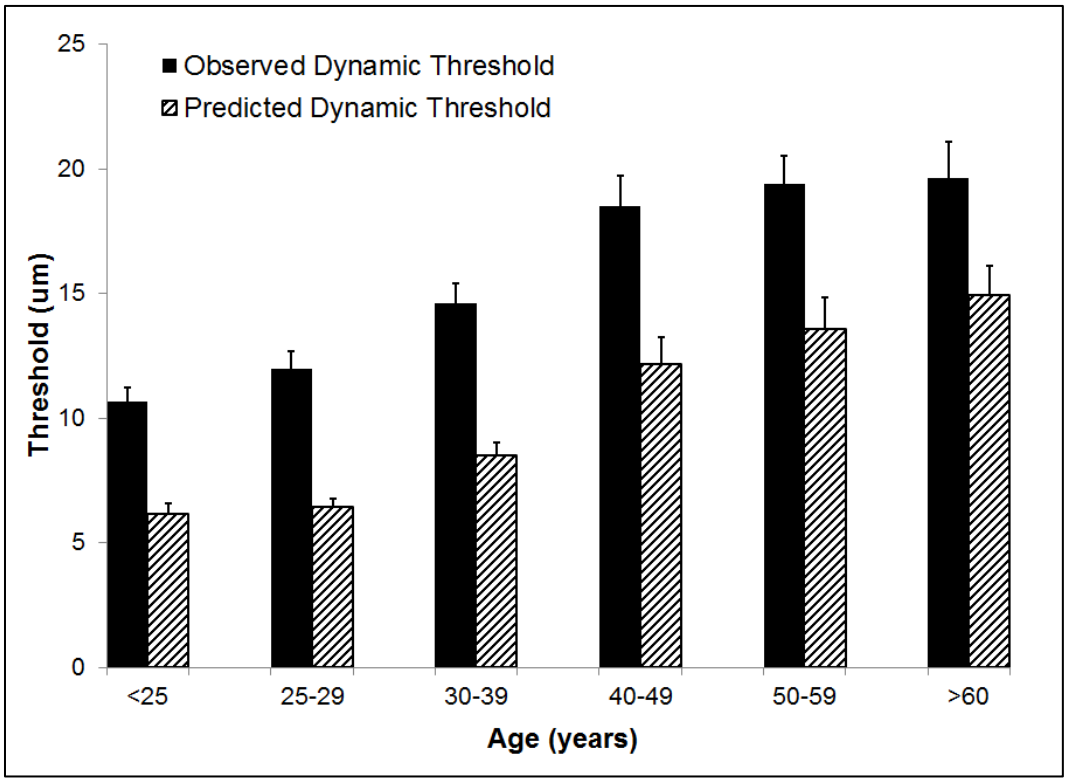

Figure 5.7 Comparison of the predicted and observed dynamic thresholds. The predicted values are always significantly smaller than the observed thresholds.

Figure 5.7 compares the predicted and observed dynamic thresholds, and the predicted values are always significantly smaller than the observed thresholds, strongly suggesting that the difference between the two measures is not simply due to reaction time. Figure 5.8 is a direct comparison between the two threshold metrics for each age group (actually a ratio of dynamic/static), and it emphasizes not only that the dynamic threshold is always greater than the static threshold, but that this value decreases with age. There is a significant difference between the youngest age group and the oldest age group ($p < 0.05$).

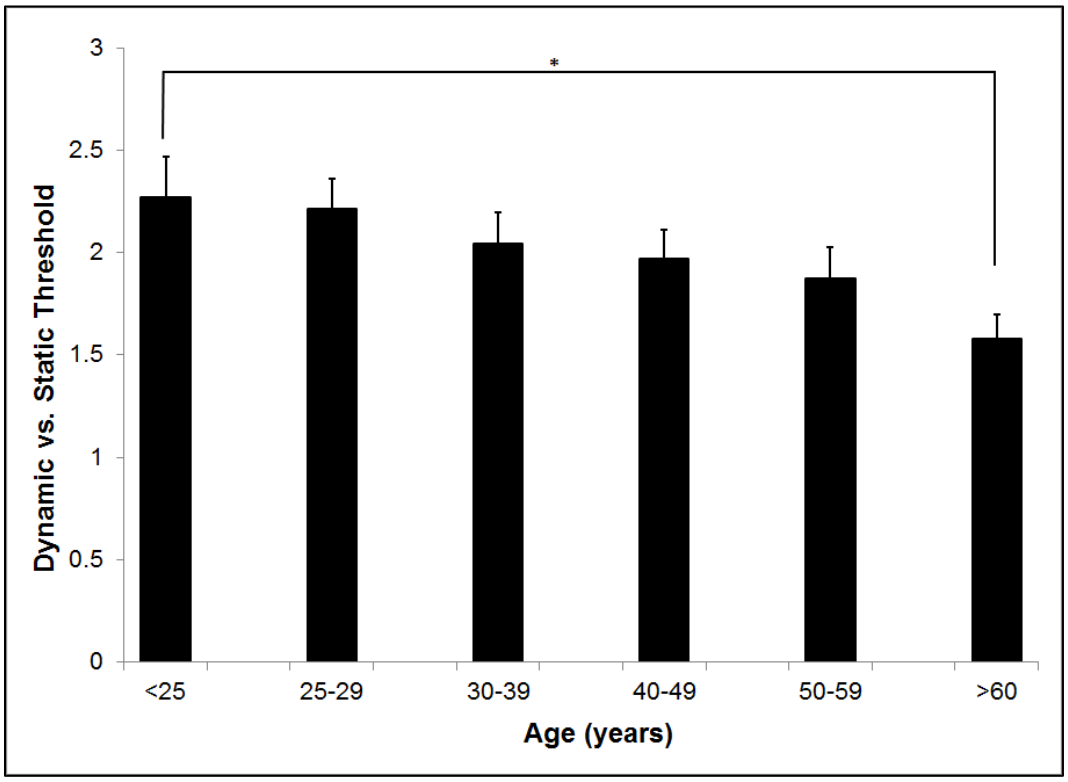

Figure 5.8 Summary of ratio of dynamic vs. static detection threshold across six age groups. Not only the dynamic threshold is always greater than the static threshold, but the dynamic vs. static ratio decreases with age. There is a significant difference between the youngest age group and the oldest age group ($p < 0.5$).

Amplitude discrimination capacity and the effects of adaptation were not altered with increases in age. Figure 5.9 summarizes the group-averaged amplitude discrimination performance obtained during amplitude discrimination task with or without pre-exposure to a conditioning stimulus (adaptation). The data demonstrate that, in the absence of single site adaptation, subjects were able to discriminate between a 100 μm and nearly 125 μm stimulus equally well for all the age groups. On the other hand, the delivery of a conditioning stimulus to one of the two stimulus sites prior to the amplitude discrimination task significantly impacted the subject's amplitude discrimination capacity, and the effects of adaptation maintained well across all the age groups. This observed impairment of amplitude discrimination capability due to adaptation is consistent with the results of previous studies (Folger et al. 2008; Tannan et al. 2008; Tannan, Simons, et al. 2007; Zhang et al. 2009). One interpretation of this impairment is that a 1 sec conditioning stimulus reduces the perceived intensity of the subsequent test stimulus to the extent that a stimulus with amplitude of approximately 170 μm (compared to 125 μm without adaptation) was perceived as nearly the same in intensity as the 100 μm stimulus. One way ANOVA proves that there is no difference in means across six age groups for the amplitude discrimination task with adaptation ($p = 0.98$) or without adaptation ($p = 0.85$). To summarize the finding across the age spectrum, there is no significant difference in amplitude discrimination performance between subjects of different age groups in discriminative capacity with or without the presence of single-site conditioning stimuli. In other words, both the metric of amplitude discriminative capacity as well as the adaptation metric (the degree to which amplitude discriminative capacity changed with the conditioning stimulus) were maintained with increases in age.

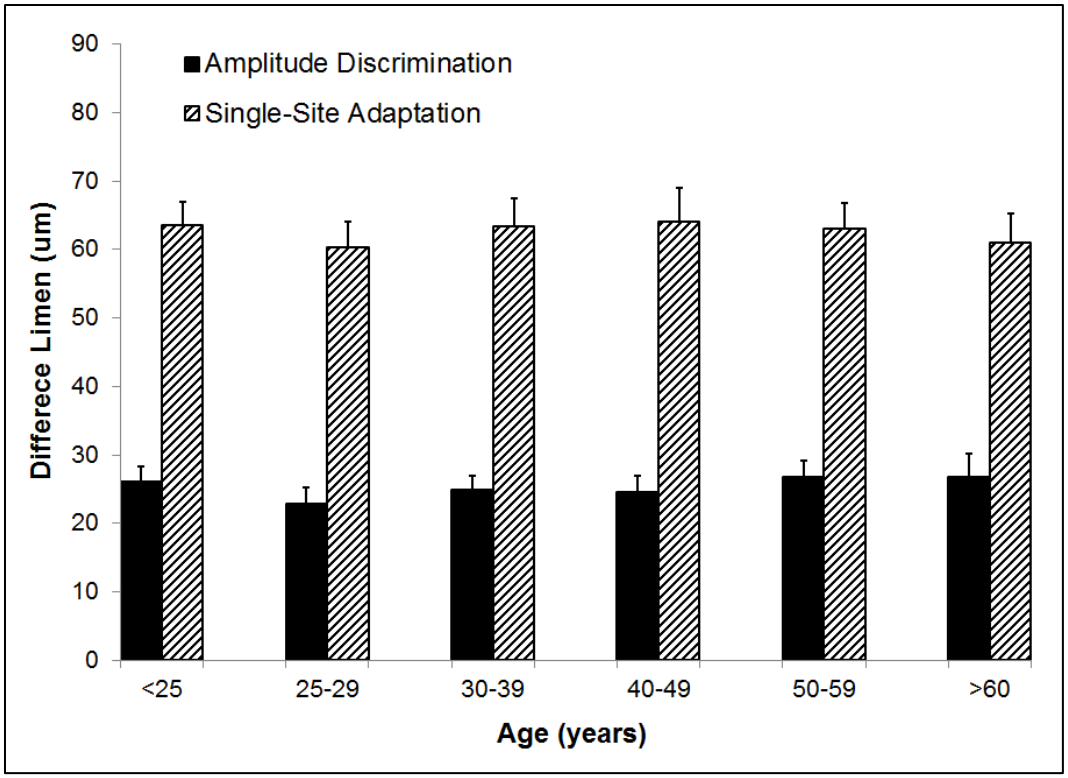

Figure 5.9 Comparison of difference limen obtained with amplitude discrimination tasks without or with single-site adaptation. There is no significant difference in means across six age groups for both metric of amplitude discriminative capacity ($p = 0.85$) as well as adaptation metric ($p = 0.98$).

5.5 Discussion

The present study evaluated the tactile information processing capacity of healthy human subjects across a wide age range (18 to 70 years). Six tests were performed to assess: (1) simple and choice RT; (2) vibrotactile detection thresholds; (3) amplitude discrimination capacity; (4) the effects of adaptation on amplitude discrimination capacity. While the results of peripherally mediated measures demonstrated significant increases in RT and detection threshold with age, the subjects' performance on the centrally mediated measures did not change. Specifically, the amplitude discrimination capacity and the impact of adaptation on performance were maintained with age. If adaptation is a metric that parallels cortical

plasticity, the results of the current study suggest that the CNS in the aging population is still capable of plastic changes, and this cortical plasticity could be the mechanism that compensates for the degradations that are known to naturally occur with age.

Among many cognitive skills, speed of information processing is considered to be especially prone to aging effects. Prior studies have shown a significant increase in reaction time between 20 year olds and 60 year olds (Fozard et al. 1994; Ratcliff, Thapar, and McKoon 2001), and this compares favorably with the results obtained in this study. In the current study, the subject's tactile information processing speed was assessed with two well established tasks: simple RT and choice RT tasks. We found that group-averaged RT was positively correlated with the average age for each group, with a correlation coefficient of 0.99 for simple RT and 0.95 for choice RT. Several studies have speculated the reasons for slowing reaction time with age, and factors other than simple speed of nerve transmission are most often cited. For example, human white matter integrity has been found to significantly correlate with information processing speed (Deary et al. 2006; Madden, Bennett, and Song 2009; Penke et al. 2010; Vernooij et al. 2009). Vernooij et al. (2009) conducted diffusion tensor imaging (DTI) scans and cognitive tasks in a sample of 860 older adults 61-92 years of age. It has been found that performance on tests that rely on processing speed degrades significantly with declining white matter integrity of the whole brain. Since many of these studies were performed on older healthy subjects without signs of mild cognitive impairment or dementia, the increase of RT might simply represent the effects of normal aging on basic cognitive function. In the context of the current study, we speculate that the increased mean RT could be the result of both decreased nerve transmission speed with age as well as the age-related decline in white matter integrity.

Increases in intra-individual variability on RT performance have been observed for older subjects compared with younger subjects. For example, it has been shown that inconsistency across trials on RT performance increases with age (Bunce et al. 2010; Gorus et al. 2008; Hultsch, MacDonald, and Dixon 2002; Hultsch et al. 2000). In this report, we found that while the group-averaged intra-individual variability remains relatively constant for the subjects younger than 50 years old, the older subjects (>50 years) have significant higher intra-individual variability. In other words, older subjects showed greater inconsistency than younger subjects in response speed. Several studies have demonstrated that performance variability has the potential to be a good indicator of neurological disturbance and may be a good marker of preclinical status of dementia. For example, Bunce et al. (2010) found greater frontal white matter lesions were associated with higher intra-individual variability in choice RT in middle-aged healthy adults. Hultsch et al. (2000) also demonstrated that performance variability was greater in patients with mild dementia than in healthy elderly subjects. As a result, measures of intra-individual variability may be a plausible behavioral indicator of aging-induced central neurological disturbances and may be able to serve as a valuable early marker of neurodegenerative disease.

Tactile detection threshold (a measure which determines the minimum stimulus intensity that can be perceived), has been documented to increase (due to decreased sensitivity) with age (Gescheider et al. 1994; Kenshalo 1986; Lin et al. 2005; Thornbury and Mistretta 1981; Verrillo 1979, 1980, 1977). In the current study, the data is consistent with prior observations and shows degraded vibrotactile sensitivity (at 25Hz) with increasing age. In order to determine if mechanisms involved in processing sub-threshold vs. threshold stimuli could be differentiated, tactile detection thresholds were collected using two different

protocols. “Static” threshold is the minimum constant-amplitude stimulus detected, and “dynamic” threshold refers to the detection threshold measured with a stimulus that is increased from zero intensity to a detectable level (Zhang et al. 2009; Zhang et al. 2011). It is noteworthy that all subjects demonstrated a dynamic threshold that was higher than their static threshold. This noticeable difference in the threshold between the two tasks is consistent with previous reports (Morioka and Griffin 2002; Zhang et al. 2009; Zhang et al. 2011). Since an argument could be made that the primary difference between the two measures is one of reaction time – dynamic threshold is reaction time dependent, while static threshold is independent of reaction time – we directly compared the actual results vs. results predicted based on this reaction time difference. As demonstrated in Figure 5.7 of Results, the difference between the observations obtained by the two methods could not be explained by reaction time alone. An alternative possibility – and one that the authors have recently proposed (Zhang et al. 2011; Favorov and Kursun 2011; Tommerdahl, Favorov, and Whitsel 2010) – is that the difference between the two threshold metrics is impacted significantly by feed-forward inhibition that is generated by the initial sub-threshold stimulus that occurs when the dynamic threshold test is ramped from a null to a detectable level. A major well-documented feature of cortical functional organization is the presence of prominent feed-forward inhibition in the input layer 4, in which local layer 4 inhibitory cells receive direct thalamocortical input and in turn suppress responses of neighboring layer 4 excitatory cells to their thalamocortical drive, thereby sharpening their RF properties (e.g., (Douglas et al. 1995; Miller, Pinto, and Simons 2001; Bruno and Simons 2002; Alonso and Swadlow 2005; Sun, Huguenard, and Prince 2006; Cruikshank, Lewis, and Connors 2007)). These inhibitory cells are more responsive to weak (near-threshold) afferent drive than are the excitatory layer 4

cells, and thus, sub-threshold or weak stimulus inputs will have the effect of *raising* the threshold at which excitatory layer 4 cells begin to respond to peripheral stimuli. Thus, the sub-threshold stimulus delivered by the dynamic threshold test actually leads to the initial inhibition, or adaptation, that ultimately requires a larger stimulus to reach detectable levels. This interesting phenomenon, and its mechanisms, is currently being investigated experimentally in vivo.

One of the interesting findings of the current study is that although the subjects' vibrotactile detection threshold went up with age, their amplitude discrimination capacity was maintained. Specifically, subjects in all age groups demonstrated a similar ability to differentiate two supra-threshold stimuli that are delivered simultaneously to the skin. It should be noted that this amplitude discrimination task was conducted at supra-threshold levels (approximately 10x normative thresholds), and all subjects had approximately the same amplitude discriminative capacity at the amplitudes used. Thus, while the decline of tactile sensitivity is considered to be influenced predominantly by peripheral factors, we speculate that the ability to discriminate between two supra-threshold stimuli is more influenced by centrally mediated factors and would are only moderately influenced by changes in the periphery. This hypothesis was derived, in part, from studies which demonstrated that localized increases in the magnitude of the SI cortical response (Simons et al. 2005; Friedman, Chen, and Roe 2008; Simons et al. 2007) paralleled the changes in the ability of human subjects to distinguish between different intensities of skin stimulation (i.e., amplitude discrimination; Francisco et al. 2008). Simons et al. (2005, 2007) investigated the optical response of squirrel monkey contralateral primary somatosensory cortex (SI) to vibrotactile stimulation (25Hz), and found that as the stimulus amplitude was increased, the

activity within the activated region of SI cortex progressively increased although the spatial extent of the activated region remained relatively constant. Rather, with increasing stimulus amplitude and duration, the region surrounding the activated cortical field became less active, suggesting that more intense and longer duration stimuli would result in more spatially resolved stimuli, which could be due to an amplitude-dependent lateral inhibitory effect that spatially funnels the responding SI neuronal population. This spatial funneling is a robust phenomenon that is at least in part due to GABAergic inhibitory neurotransmission (Juliano et al. 1989). Analogously, the observations of human psychophysical studies have demonstrated that the ability of a subject to accurately localize and discriminate a flutter stimulus on the skin is determined by the locus and clarity of the neuronal population response within the topographically organized SI network (LaMotte and Mountcastle 1975, 1979). In other words, at supra-threshold stimuli, lateral inhibition plays an important role in discriminating between the cortical loci that are activated on adjacent digit tips by the amplitude discrimination task. Systemic cortical alterations that impact the mechanisms involved in lateral inhibition would have significant impact on amplitude discriminative capacity, and thus, we would predict that amplitude discriminative capacity would be diminished with the systemic cortical alterations that are characteristic of neurodegenerative disorders.

To investigate potential changes in cortical plasticity with normal aging, the effect of single site adaptation on amplitude discrimination capacity was measured. Previous studies using this adaptation metric demonstrated that a conditioning stimulus delivered to one of the two sites before the amplitude discrimination task significantly altered a subject's ability to determine the actual difference between the two stimuli (Tannan et al. 2008; Tannan, Simons,

et al. 2007) by introducing a confound. In other words, the conditioning stimulus makes the subsequent stimulus, at the conditioned site, feel weaker and consequently, amplitude discriminative capacity is reduced. Neurophysiological studies have demonstrated that the effects of reduced intensity due to adapting stimulation are possibly attributable to a reduction in the responsivity of central neurons after prolonged or repetitive stimulation. More specifically, Lee and Whitsel (Lee and Whitsel 1992) and Lee et al. (Lee, Whitsel, and Tommerdahl 1992) found that the majority (58%) of the SI neurons sampled showed a decreased response to repetitive stimulation (3-5 Hz) of their receptive fields. In that report, it was proposed that the glutamate-mediated excitatory effects on NMDAR are to a large extent responsible for the appreciable capacities of cortical neurons to modify their physiological properties with repetitive sensory experience. When the single adaptation measure is examined across a number of subject populations with compromised CNS - as may be the case with a neurodevelopmental disorder: autism (Tannan et al. 2008), acute pharmacological block (Folger et al. 2008) or a chronic pain condition (Zhang et al. 2011) - the adaptation metric is significantly diminished from that of the control population. These findings suggest that the method could be viewed as a potential indicator or marker of systemic cortical alterations, as adaptation, at this short duration time scale, is impacted by a number of factors. In particular, these factors include GABA and NMDA receptor mediated neurotransmission, and neuron-glial interactions (for discussion, see (Folger et al. 2008; Francisco et al. 2008; Tannan et al. 2008; Tannan, Simons, et al. 2007; Tommerdahl, Favorov, and Whitsel 2010; Tommerdahl, Tannan, Cascio, et al. 2007; Zhang et al. 2009; Zhang et al. 2011)).

In the literature, evidences from a wide range of studies have demonstrated that while adult brain is declining with age, it is still capable of plastic changes. For instance, in a series

of studies, Dinse and colleagues have reported that experimental or environmental stimulations could induce use-dependent plasticity in older animal as well as human subjects at both cortical and behavioral level (Kattenstroth et al. 2010; Kalisch et al. 2009; Kalisch, Tegenthoff, and Dinse 2008; Dinse et al. 2006; Dinse 2006, 2005; Li and Dinse 2002; Hilbig et al. 2002). Specifically, it has been found that old rats exposed to enriched environment showed complete recovery from the age-related enlargement of RFs of the hindpaw in somatosensory cortex typically found in animals housed in standard conditions (Hilbig et al. 2002). At the behavioral level, repetitive sensory stimulation procedures resulted in improvement of tactile acuity in elderly individuals, a phenomenon based on synaptic plasticity (Dinse et al. 2006; Dinse 2005). In this study, we found that the effects of adaptation remain relatively constant across healthy populations regardless of age. Since adaptation is an important feature of cortical information processing that apparently remains intact with normal aging, it could be an important feature to assess in the aging population. Deviations from normative values could be an early indicator of neurodegenerative disease; studies directly addressing this issue are currently ongoing and will be reported in the near future.

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